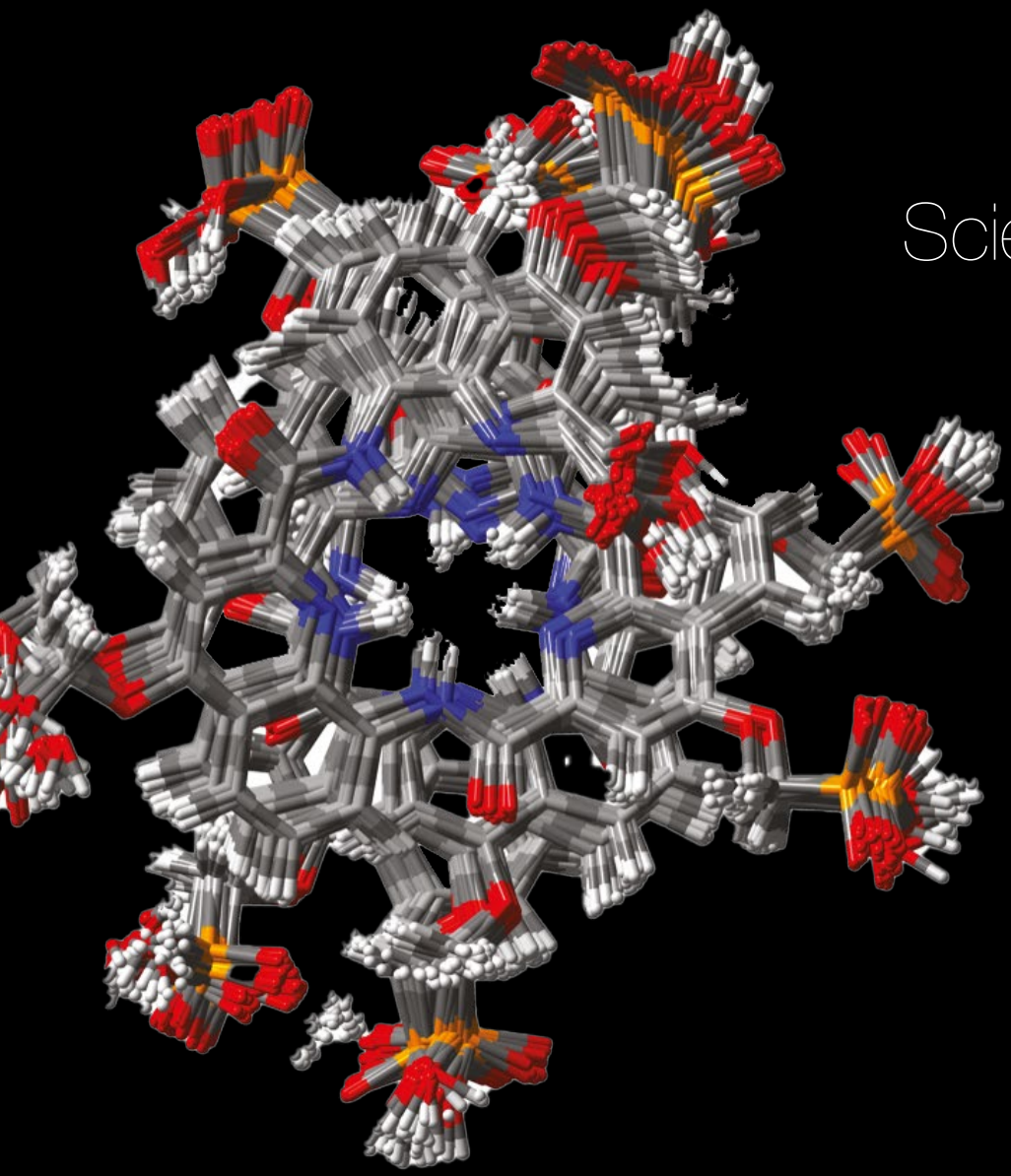
Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

IECB



Scientific Report

2021

université de BORDEAUX

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

cnrs

Prix Liliane Bettencourt *pour les sciences du vivant*

Fondation Bettencourt Schueller

Reconnue d'utilité publique depuis 1987

Publication director: Valérie Gabelica **Graphic design:** A to B communication & Delphine Fleury
Photo credits: Frédéric Rosu (front cover), Hugette Vanlierde, Claire-Hélène Biard (photo event), Yves Théobald (building, portraits), Marc Grémillon (portraits), Lionel Lizet (IECB-CGFB technology platform).

Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

Scientific Report

2021

Director's Foreword

Dr. Valérie GABELICA
Research Director (DR2), Inserm

Looking to the future

After Jean-Yves Lallemand, Jean-Jacques Toulmé, Jean-Louis Mergny and Rémi Fronzes, it's an honor for me to serve as the fifth executive scientific director of the Institut Européen de Chimie et Biologie. I am accompanied in this mission by Antoine Loquet, adjunct director, and benefit from the invaluable help of our administrative director Sylvie Djian, our platforms director Brice Kauffmann, and group leaders serving in our steering committee.

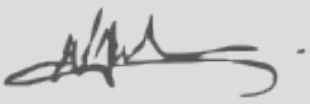
More than twenty years ago, the IECB founders had a vision, revolutionary in France at the time. The first principle was to give full scientific and financial independence to group leaders, independently of their career stage (a principle which really took hold in Europe in 2007 with the ERC), with a selection of group leaders by a scientific advisory board (SAB) based solely on the project and the personal qualities of the candidate. The second principle was to promote interdisciplinary research at the crossroads between chemistry and biology, to favor new discoveries with impact for health and medical research. For that, teams are hosted not just for a single project, but rather for a longer period of around 10 years, subject to the approval of our SAB.

The IECB has thus hosted no less than 35 groups over the years, 14 groups with the IECB label in 2021. You will read herein about their research and latest results. Although the topics are broadly classified as organic chemistry, biophysics, structural biology and cell biology, there are no real boundaries between the fields, as illustrated by several collaborative publications. For example, the Guichard, Mackereth and Gabelica groups studied the biophysics of synthetic oligourea foldamer self-assembly (*Chem. Commun.* 2021, 57, 9514), and the Royou and Friscourt groups studied the impact of click-chemistry chemical reporters on bacterial enzymes (*ACS Chem. Biol.* 2021, 16, 2307). I also take the opportunity here to congratulate Frédéric Friscourt for obtaining a tenured teaching position at the Université de Bordeaux. Frédéric is now affiliated to the ISM (Institut des Sciences Moléculaires).

And the IECB adventure will continue in the future. In October 2020, our SAB recommended two new candidates, and we are happy to announce that Yann Fichou and Pierre Maisonneuve will be starting their groups officially in 2022, thanks to an ERC Starting Grant funding for Yann, and a Fondation pour la Recherche Médicale funding for Pierre. We are happy to celebrate that *Yann Fichou is the 10th group leader to be awarded an ERC grant!* We also bid farewell to our group leaders David Santamaria, who was offered a senior position at the Centro de Investigación del Cáncer (CIC) at the University of Salamanca, and to Anne Royou and Derek McCusker who will move to brand-new lab premises at the Institut de Biochimie et Genetique Cellulaires (IBGC) here in Bordeaux.

The adventure will also continue in the following years thanks to major restructuring of buildings on the University of Bordeaux campus, which will free up some space in IECB for new teams to join us and work at the chemistry-biology interface. Three outstanding candidates were recommended by our SAB in October 2021, and in 2022 we will issue a new call as well, with a priority in recruiting new group leaders in the field of cellular and molecular biology.

Valérie Gabelica



The Institut européen de chimie et biologie (IECB) is a research team incubator placed under the joint authority of the CNRS, the Inserm and the Univ. Bordeaux. It was created in 1998 with the support of the Aquitaine Regional Council to provide promising European chemists and biologists with an environment designed to facilitate the development of first-class interdisciplinary research programs, in collaboration with international public and private research centres.

IECB's International Scientific Advisory Board guides the selection and periodic evaluation of the team leaders. After a probative period of two years, research teams are then hosted for a maximum of 10 years. During their stay at IECB, teams enjoy full financial and managerial autonomy and benefit from state-of-the-art facilities and dedicated technical expertise through IECB's technology platforms in structural biology and preparative and analytical techniques.

The IECB is the largest research team incubator in France, with 14 research teams accounting for 180 researchers and expert technicians.

The company Ureka (Immupharma Group) is hosted at the institute.

Contents

The IECB International Scientific Advisory Board, chaired by Dr Moshe YANIV, interviewed candidates from all over the world for group leader positions.

Dr. Moshe YANIV
Chairman, Institut Pasteur,
Paris, France

Dr. Stephen CUSACK
EMBL, Grenoble, France

Dr. Witold FILIPOWICZ
Friedrich Miescher Institute for
Biomedical Research, Basel, Switzerland

Dr. Bernd GIESE
University of Fribourg, Switzerland

Dr. Anne HOUDUSSE JUILLE
Institut Curie, Paris, France

Pr. Roeland NOLTE
Radboud University, Nijmegen,
Netherlands

Pr. Yves POMMIER
National Cancer Institute,
Bethesda, USA

Dr. Claude SARDET
Institut de Recherche en Cancérologie
de Montpellier, France

Pr. Helma WENNEMERS
ETH, Zurich, Switzerland

Organisational Structure

Board Members

International scientific advisory board (ISAB)

Dr. Moshe YANIV President
Institut Pasteur, Paris, France

Dr. Stephen CUSACK
EMBL, Grenoble, France

Dr. Witold FILIPOWICZ
Institut Friedrich Miescher, Basel, Switzerland

Dr. Bernd GIESE
Departement of Chemistry, University of Basel, Switzerland

Dr. Anne HOUDUSSE JUILLE
Institut Curie, Paris, France

Pr. Roeland NOLTE
Radboud University Nijmegen, Netherlands

Pr. Yves POMMIER
National Cancer Research, NIH, Bethesda, USA

Dr. Claude SARDET
Institut de Recherche en Cancérologie de Montpellier (IRCM), France

Pr. Helma WENNEMERS
ETH Zurich, Suisse

Former ISAB members

Dr Herbert WALDMANN
Max Planck Institute of Molecular Physiology, Dortmund, Germany

Dr. Daniel SCHIRLIN
Sanofi Aventis, Paris, France

Prof. Dinshaw PATEL
Memorial Sloan-Kettering Cancer Center, New York, USA (2009-2016)

Dr. Daniel LOUVARD
Institut Curie, Paris, France (1999-2014)

Pr. Iain D. CAMPBELL
Departement of Biochemistry, University of Oxford, UK (1999-2013)

Dr. Simon CAMPBELL
Royal Society of Chemistry, London, UK

Pr. Claude HÉLÈNE
Muséum National d'Histoire Naturelle, Paris, France (1999-2003)

Pr. Georges HUEZ
Université Libre de Bruxelles, Brussels, Belgium (2000-2005)

Pr. Steven LEY
Departement de Chemistry, University of Cambridge, UK (1999-2005)

Pr. Helmut RINGSDORF
Institut für Organische Chemie, Johannes Gutenberg Universität, Mainz, Germany (1999-2006)

Pr. Fritz ECKSTEIN
Max Planck Institute for Experimental Medicine, Göttingen, Germany (2003-2006)

Pr. Jack BALDWIN
Departement of Chemistry, University of Oxford, UK (2005 - 2007)

Pr. Wilfred van GUNSTEREN
Laboratory of Physical Chemistry, ETH, Zürich, Switzerland (1999-2007)

Pr. François DIEDERICH
Department of Chemistry and Applied Biosciences, ETH, Zürich, Switzerland (2006-2008)

Pr. Jean-Yves LALLEMAND
Institut de Chimie des Substances Naturelles, CNRS Gif-sur-Yvette, France (1999-2010)

Board of directors

Dr. Valérie GABELICA Executive Scientific Director, Research Director, team leader U1212 (Inserm)

Dr. Antoine LOQUET Deputy Scientific Director, Research Director, team leader (CNRS), UMR5248

Mrs. Sylvie DJIAN Administrative Director (CNRS)

Former directors

Dr. Rémi Fronzes Former Executive Scientific Director (2019-2020)

Dr. Jean-Louis MERGNY Former Executive Scientific Director (2015-2018)

Dr. Jean-Jacques TOULMÉ Former Executive Scientific Director (2001-2014)

Pr. Jean-Yves LALLEMAND Former Executive Scientific Director (1998-1999)

Pr. Léon GHOSEZ Former Deputy Scientific Director (1998-2008)

Steering committee

Mrs. Sylvie DJIAN Administrative Director (CNRS)

Dr. Rémi FRONZES Team leader
Research Director (CNRS), UMR5234

Dr. Valérie GABELICA, Team leader
Research Director (Inserm), U1212

Dr. Gilles GUICHARD Team leader
Research Director (CNRS), UMR5248

Dr Yaser HASHEM Team leader
Research Director (Inserm), U1212

Dr. Axel INNIS, Team leader
Research Director (Inserm), U1212

Dr. Brice KAUFFMANN Head of IECB's technology platforms
Engineer (CNRS) UMS3033

Dr. Antoine LOQUET Team leader
Research Director (CNRS), UMR5248

Board of trustees

Centre National de la Recherche Scientifique
3 rue Michel-Ange, 75794 Paris CEDEX 16

Institut National de la Santé et de la Recherche Médicale
101 rue de Tolbiac, 75654 Paris CEDEX 13

Univ. Bordeaux
35 Place Pey Berland, 33000 Bordeaux

Organisational Chart

Research teams

- Board of directors
- Steering committee

Institut Européen de Chimie et Biologie
I E C B

- Board of trustees
- International scientific advisory board

Pole 1 – Structural biology

- Structure and Function of Bacterial Nanomachines
  Dr. Rémi Fronzes
- RNA Processing and translation regulation in pathogens and hosts
  Dr. Yaser Hashem
- Translational Regulation of Gene Expression
  Dr. Axel Innis
- Structural Biology of Biofilms
  Dr. Petya Krasteva
- Membrane Protein Mechanisms
  Dr. Nicolas Reyes

Pole 2 - Organic & bioorganic chemistry

- Chemical Neuroglycobiology
  Dr. Frédéric Friscourt
- Peptidomimetic Chemistry
  Dr. Gilles Guichard
- Chemical Biology of membrane proteins
  Dr. Emmanuelle Thinon

Pole 3 - Biophysics

- Single-molecule Biophysics
  Dr. Mikayel Aznauryan
- Mass Spectrometryof Nucleic Acids & Supramolecular Complexes
  Dr. Valérie Gabelica
- Solid-state NMR of Molecular Assemblies
  Dr. Antoine Loquet

Pole 4 - Molecular & cellular biology

- Dynamics of cell growth & cell division
  Dr. Derek McCusker
- Control & dynamics of cell division
  Dr. Anne Royou
- Novel mediators in lung oncogenesis
  Dr. David Santamaria

Associate members

- Organic & medicinal chemistry
  Pr. Léon Ghosez

Administrative services
UMS3033 & US001

Technology platforms
UMS3033 & US001

- Structural biology
- Preparative & analytical techniques

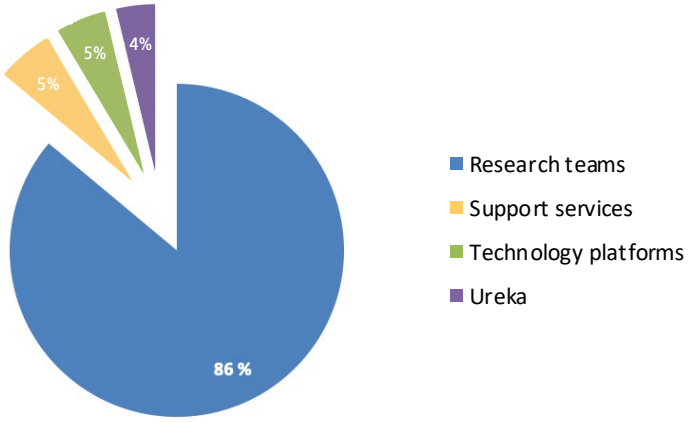
Technology transfer & start-ups

URE kA

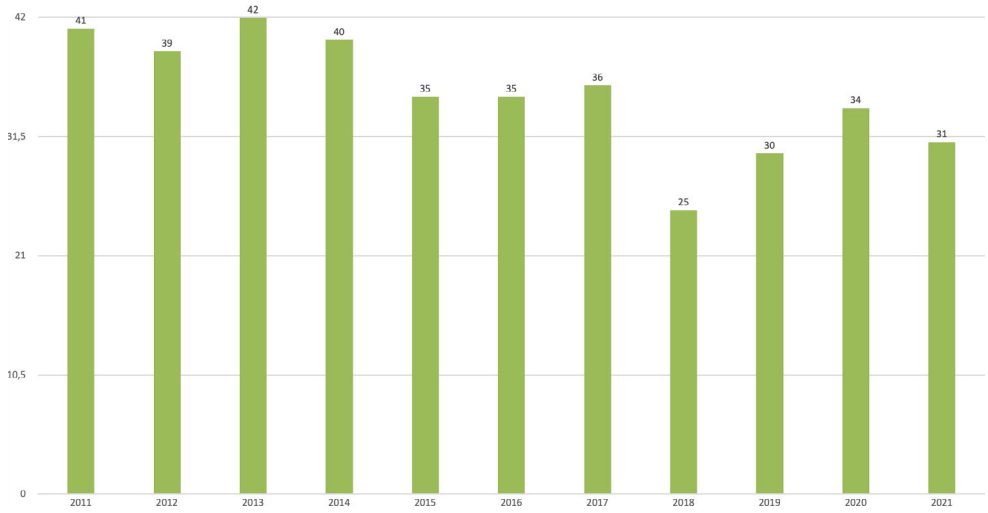
2021 Key Figures

In 2021, 174 people were part of the IECB: 187 research staff, 19 employees within the IECB's support services unit and 7 employees of the companie Ureka. Young researchers (Master and PhD students, postdoctoral researchers) represent 59% the IECB research staff. This population largely contributes to gender equality and internationalization at IECB. It also testifies to the attractiveness of the institute.

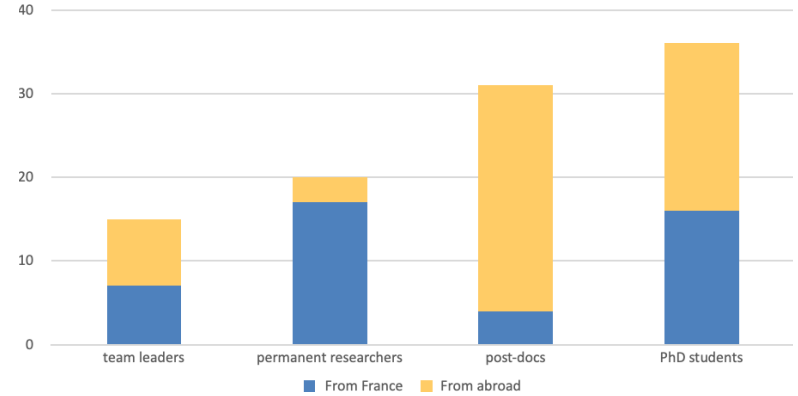
IECB staff by professionnal category



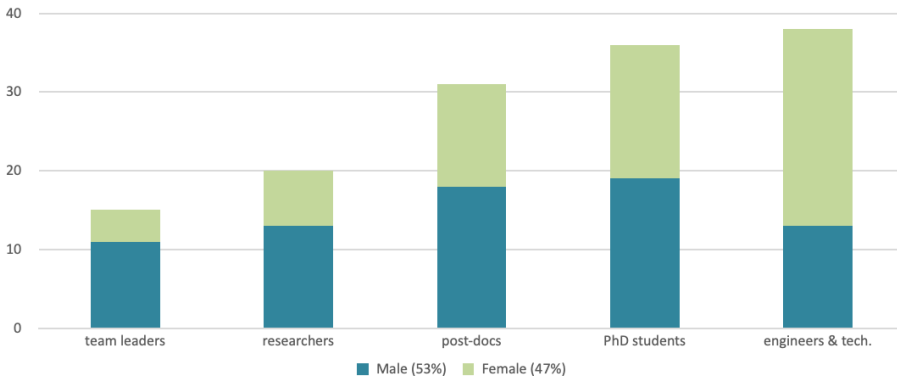
Number of postdoctoral researchers over the past 10 years



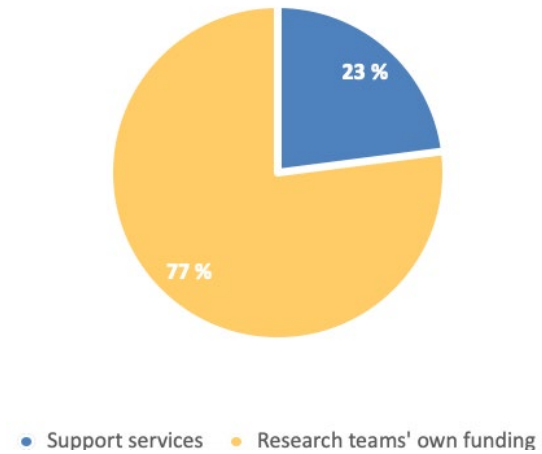
IECB researchers and students by nationality & professional category



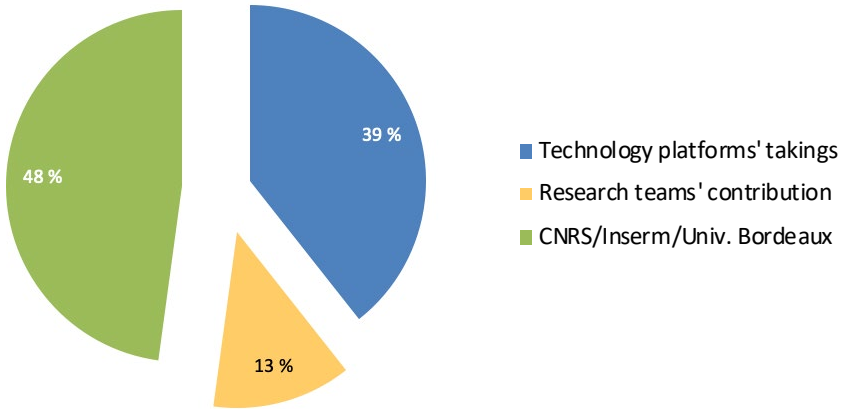
IECB research staff by gender & professional category



IECB's 2021 budget



Support services funding



The budget of the institute, which amounts to 8,5 million euros including salaries, can be divided into two separate parts: the budget of the support services (UMS3033/US001) and the research teams' own resources.

The first one is mainly granted by the trustees (CNRS, Inserm, Université de Bordeaux), while the other comes from public and private research grants and contracts.

SUPPORT SERVICES (UMS3033 & US01)

Support services at IECB consist of staff in administration and finance, infrastructure and maintenance, as well as 10 engineers and technicians dedicated to IECB's technology platforms. The support services unit UMS3033 & US01 is jointly funded by the CNRS, the Inserm and the Univ. Bordeaux, and receives financial support from the Nouvelle Aquitaine Regional Council. Research teams also contribute to financing those general services.

Administration and finance

Administrative director
Sylvie DJIAN, IR, CNRS
Executive assistant officer
Claire-Hélène BIARD, AI, Inserm
Accounting and administration officers
Laetitia COINTEMENT, Tech, Inserm
Catherine DUPRAT, Tech, Inserm
Laurent KUBICKI, Tech, Inserm
Sandra LAVENANT, Tech, Univ. Bordeaux
Amélie STOTZINGER, Tech, Inserm
IT management
Gérald CANET, IE, Inserm
Eric ROUBIN, Tech, Inserm
Infrastructure officer
Patrice DUBEDAT, AJT, Univ. Bordeaux

Structural biology facilities

Head of structural biology facilities and crystallography engineer
Brice KAUFFMANN, IR, CNRS
Crystallography engineer
Stéphane MASSIP, IE, Univ. Bordeaux
Nuclear magnetic resonance engineer
Estelle MORVAN, IE, CNRS
Mass spectrometry engineer
Frédéric ROSU, IR, CNRS
Surface plasmon resonance engineer
Laetitia MINDER, AI, Inserm
Electron microscopy engineer

Biochemistry and molecular biology engineer
Laure BATAILLE, IR, Univ. Bordeaux
Jean-Michel BLANC, IE, Inserm
Biochemistry and molecular biology technicians
Thierry DAKHLI, Tech, Inserm
Myriam MEDERIC, Tech, Inserm
Quality approach
Loïc KLINGER, AI, CNRS

Dr. Yann Fichou will joined IECB as group leader in September 2022.

Yann Fichou's research focus on the molecular mechanisms underlying neurodegenerative diseases. He has a specific interest for the tau protein, an intrinsically disordered protein present in the brain where it regulates the microtubule activity. Tau is directly implicated in several neurodegenerative diseases, including Alzheimer's disease, in which it forms amyloid aggregates. Yann's group studies the formation of these amyloids, the factors that determine their structure as well as their pathological activity. The group adopts a multi-technique approach in which they use a large array of biochemical and biophysical methods including EM, NMR and EPR. They have a particular expertise and interest in advanced methods of EPR applied to protein sciences.

Yann Fichou received in 2015 his PhD from the Université Grenoble Alpes under the supervision of Martin Weik at the Institut de Biologie Structurale (IBS). He carried out a first postdoc in the lab of Martina Havenith at Ruhr-Universität Bochum (RUB, Germany) a second postdoc at the University of California Santa Barbara (UCSB) in the group of Songi Han. Since 2020, Yann Fichou is a CNRS Chargé de Recherche at the institute de Chimie et Biologie des Membranes et Nano-objets (CBMN) in Bordeaux.

Dr. Pierre Maisonneuve joined IECB as Group Leader in April 2022.

The research interests of Pierre Maisonneuve are to decipher the molecular mechanisms of protein kinases and pseudokinases in human signaling. His group will mainly focus on a particular family of pseudokinase-containing receptors that are implicated in many human diseases, such as cancer. Therefore, they are very promising therapeutic targets. However, much remains to be learned about the mechanism by which they transduce external signals across the membrane to trigger intracellular downstream signaling and affect the cell function. To this aim, his group combines state-of-the-art structural biology (Cryo-EM, X-Ray crystallography and NMR), functional characterization of proteins and development of new chemical tools, which can serve as proof-of-concept for new therapeutical acvenues.

Pierre Maisonneuve has completed his PhD in the group of Dr. Wolff at the Pasteur institute in Paris. He then moved as a postdoctoral researcher in the laboratory of Dr. Sicheri at the Lunenfeld-Tanenbaum research Institute in Toronto.

His team is affiliated to the laboratory of chemistry and biology of membranes and nano-objects (CBMN, CNRS, UMR 5248, University of Bordeaux).

Research Teams & Output

European Research Council

Structure and Function of Bacterial Nanomachines

Dr. Rémi Fronzes
Research Director (DR2), CNRS

Rémi Fronzes has a long-term research experience in biochemistry and structural biology of macromolecular assemblies. He trained as a membrane protein biochemist during his PhD in Bordeaux (France). In 2005, he moved to Gabriel Waksman's laboratory at the Institute of Structural and Molecular Biology in London (UK) to work as a postdoctoral research associate. In 2009, he was appointed as a junior research scientist at the CNRS and as a group leader at institut Pasteur, in Paris (France). In 2011, RF was awarded an ERC (European Research Council) starting grant. In 2015, Rémi Fronzes was awarded a "Chaire d'excelence Senior" by the university of Bordeaux and Aquitaine regional Council. He moved his research group to IECB and CNRS unit UMR 5234 « Microbiologie Fondamentale et Pathogénicité in 2016. In 2017, RF was awarded an ERC consolidator grant. He is the coordinator of the EquipEx+ project NanoCryoCLEM awarded in 2020.

Research team

Dr. Rémi FRONZES Research Director DR2, (CNRS)
Dr. Esther MARZA Maître de conference (Univ. Bordeaux)
Prof. Jean-Paul BOURDINEAUD Professeur (Univ. Bordeaux)
Dr Leonardo TALACHIA ROSA Post-doctoral fellow ERC
Dr Pauline PONY Post-doctoral fellow ERC
Pierre NOTTELET PhD Student ANR
Robin ANGER PhD student ERC
Nina LOPEZ-LOZANO PhD Student (Univ. Bordeaux)
Dr Pierre MAISONNEUVE Visiting scientist Research scientist, (University of Toronto)
Laure BATAILLE Visiting Scientist Engineer, CIRI, (INSERM, Lyon)

This team is part of the unit "Microbiologie fondamentale et pathogénicité" (MFP), CNRS UMR5234/Univ. Bordeaux

Bacteria are extremely adaptable and able adjust their lifestyle very quickly when these changes occur. One dramatic illustration of this capacity is the spread of antibiotic resistance among bacterial pathogens. During the last decade, the emergence of multi-resistant bacteria, which are resistant to several treatments, led to increase mortality caused by common infections. The 2014 report on antimicrobial resistance from the World Health Organization warns against the beginning of a "post-antibiotic" era, when most of the bacterial pathogens will become resistant to all treatments available.

In this context, it is crucial to fully understand the molecular mechanism of bacterial adaptability to ultimately target and limit this ability. To survive in a changing environment, bacteria have to resist to stresses induced by these changes and ultimately to adapt their lifestyle if these changes persist. These two processes are almost contradictory since the first aims at maintaining cell integrity while the second allows long term variability through the acquisition of new traits.
For 10 years, the team engaged several lines of research on this topic in the lab, first at institut Pasteur and from 2016 within the MFP unit and at the Institut Européen de Chimie et Biologie (IECB) in Bordeaux. Over the last 5 years, we focused our research on the main projects listed below. The lab has also been instrumental in setting up a state of the art cryo-electron microscopy (CryoEM) facility at IECB. We have several on-going collaborations related to our expertise in CryoEM. We are also involved in technological development projects such as the implementation of super-resolution correlative microscopy in cryo conditions.

Project 1: Natural transformation and gene repair in bacterial pathogens (Funded by ERC)

In this project, we want to understand how DNA can be uptaken and recombined in the bacterial genome during bacterial transformation.
Natural genetic transformation, first discovered in *Streptococcus pneumoniae* by F. Griffith in 1928, is observed in many Gram-negative and Gram-positive bacteria. This process promotes genome plasticity and adaptability. In particular, it enables many human pathogens such as *Streptococcus pneumoniae, Neisseria gonorrhoeae* or *Vibrio Cholerae* to acquire resistance to antibiotics and/or to escape vaccines through the binding and incorporation of new genetic material. While it is well established that this process requires the binding, internalization of external DNA and its recombination in the bacterial genome, the molecular details of these steps are unknown. In this project, we aim at acquiring a detailed understating of each of these steps. We discovered a new appendage at the surface of *S. pneumoniae* cells and showed that this appendage is similar in morphology and composition to appendages called Type IV pili commonly found in Gram-negative bacteria. We demonstrated that this new pneumococcal pilus is essential for transformation and that it directly binds DNA **(PLOS Pathogens 2013 and 2015)**. We are also actively studying the DNA translocation apparatus. We isolated most of its components and are in the process of determining their structure and studying their function *in vitro* and *in vivo*. Finally, we identified a new key ATPase involved in the recombination process. We determined the crystal structure of this protein and identified its function in vitro and in vivo in collaboration with Patrice Polard's team in Toulouse (France) **(Nature communications, 2017)**. We also explored the initiation and molecular mechanism of the recombination event. We determined the structure of RecA filaments from *S. pneumoniae* and revealed the structural basis of its interaction with its loader on ssDNA during transformation (called DprA) **(Manuscripts in preparation)**. Finally, we are also exploring the architecture of the transformation apparatus in its native cellular environment using Cryo-tomography and correlative microscopy approaches.

Project 2: Bacterial competition systems (Type 6 and type 7 secretion systems) (funded by the IDEX/regional Chair).

The bacterial Type 6 secretion (T6S) system is one of the key players for microbial competition, as well as an important virulence determinant during bacterial infections. It assembles a nano-crossbow-like structure that propels an arrow made of Hcp tube and VgrG spike into the cytoplasm of the attacker cell and punctures the prey's cell wall. The nano-crossbow is stably anchored to the cell envelope of the attacker by a membrane core complex. In collaboration with Eric Cascales' laboratory in Marseille (France), we recently have shown that this membrane complex is assembled by the sequential addition of three proteins -TssJ, TssM and TssL- and presented a structure of the fully assembled complex **(Nature 2015)**. Since our arrival at IECB and MFP, we solved the cryoEM structure of this complex **(EMBO J. 2019)**. We also solved the cryoEM structure of another key element of the T6S system, the baseplate **(Nature microbiology 2018)** and of the T6SS substrate from pathogenic *Escherichia* coli in complex with the T6SS spike **(EMBO J. 2020)**.

While at institut Pasteur, our group started to work on type 7 secretion systems (T7SS). These systems are mostly found in mycobacteria and other Gram-positive bacteria such as *Staphylococcus aureus or Bacillus subtilis*. While it is well established that mycobacterial T7SS are directly used in virulence, their exact function in other Gram-positive bacteria was unclear. We recently revealed that the T7SS found in B. subtilis is an anti-microbiobal device used by these bacteria to kill other Gram-positive bacteria **(BioRviv 2020)**. We also performed an in-depth biochemical study and solved the crystal structure of a key component of this system (YukC). Overall, our work shows that B. *subtilis* Yuk T7SS is a bona fide and functional T7SS that can be used a model system to study T7SSs.

Project 3: Metabolic adaptability of bacterial pathogens (funded by the ERC)

Acetaldehyde-alcohol dehydrogenase (AdhE) enzymes are a key metabolic enzyme in bacterial physiology and pathogenicity. They convert acetyl-CoA to ethanol via an acetaldehyde intermediate during ethanol fermentation in an anaerobic environment. This two-step reaction is associated to NAD+ regeneration, essential for glycolysis. The bifunctional AdhE enzyme is conserved in all bacterial kingdoms but also in more phylogenetically distant microorganisms such as green microalgae. It is found as an oligomeric form called spirosomes, for which the function remains elusive. We used cryo-electron microscopy to obtain structures of *E. coli* spirosomes in different conformational states. We showed that spirosomes contain active AdhE monomers, and that AdhE filamentation is essential for its activity *in vitro* and function *in vivo*. The detailed analysis of these structures provides insight showing that AdhE filamentation is essential for substrate channeling within the filament and for the regulation of enzyme activity. This work was published in **Nature communications in 2020**.

Project 4: Structure and function of a mycoplasma antibody cleavage device (funded by the ANR, in collaboration Yonathan Arfi, INRA, Bordeaux)

Mycoplasmas cause various chronic diseases in animals and humans. They have evolved strategies to evade the host immune response, including the Mycoplasma Ig Binding (MIB)- Mycoplasma Ig Protease (MIP) antibody degrading system. The Fab domain of many types of immunoglobulins is recognized by MIB. This interaction allows the recruitment of the serine protease MIP, which cleaves the VH domain of the antibody. To understand the molecular basis of this system, we have solved the structure of the ternary complex Fab-MIB-MIP antibody degrading system by cryo-electron microscopy. The structure of the complex between MIB, MIP and the Fab fragment of a goat IgG has been solved to a 3 Å resolution, by single particle cryoEM. Together with biochemical and in vivo data, our work reveals very original binding mechanism of the complex to the antibody **(Science Advances, 2020)**.

Project 5: Development of super-resolution cryo-correlative microscopy

The project 5 started very recently in collaboration with the laboratories of Daniel Choquet (IINS), Brahim Lounis, (LP2N) Gregory Giannone (IINS), Bordeaux imaging center and the UMS of the IECB. The major challenge in cell and structural biology today is to combine two cutting-edge technologies, super-resolution fluorescence microscopy and cryoEM, to enable a new revolution in the determination of atomic structure and the understanding of the function of molecules in their natural context. Multimodal or correlative microscopy approaches combining the power of high-resolution optical and electronic microscopy are at the forefront of technology at the national and international level. This technological development will make it possible to go beyond the limits of existing technologies and will revolutionize our understanding of the molecular mechanisms of living organisms, particularly in the fields of neurobiology, cancerology and the study of pathogens such as parasites, bacteria that are multi-resistant to antibiotics or emerging viruses. Rémi Fronzes is the coordinator of an EquipEx proposal awarded in 2020 focusing on this project. He is also the coordinator of a CPER project for IECB, including equipment that will be essential to this project.

Selected publications

1. Kumar, A.; Planchais, C.; Fronzes, R.; Mouquet, H.; Reyes, N. Binding Mechanisms of Therapeutic Antibodies to Human CD20. *Science* **2020**, 369 (6505), 793-799. https://doi.org/10.1126/science.abb8008.

2. Pony, P.; Rapisarda, C.; Terradot, L.; Marza, E.; Fronzes, R. Filamentation of the Bacterial Bi-Functional Alcohol/Aldehyde Dehydrogenase AdhE Is Essential for Substrate Channeling and Enzymatic Regulation. *Nat Commun* **2020**, 11 (1), 1426. https://doi.org/10.1038/s41467-020-15214-y.

3. Jurėnas, D.; Rosa, L. T.; Rey, M.; Chamot-Rooke, J.; Fronzes, R.; Cascales, E. Mounting, Structure and Autocleavage of a Type VI Secretion-Associated Rhs Polymorphic Toxin. *Nat Commun* **2021**, 12 (1), 6998. https://doi.org/10.1038/s41467-021-27388-0.

4. Flaugnatti, N.; Rapisarda, C.; Rey, M.; Beauvois, S. G.; Nguyen, V. A.; Canaan, S.; Durand, E.; Chamot-Rooke, J.; Cascales, E.; Fronzes, R.; Journet, L. Structural Basis for Loading and Inhibition of a Bacterial T6SS Phospholipase Effector by the VgrG Spike. *EMBO J* **2020**, 39 (11), e104129. https://doi.org/10.15252/embj.2019104129.

5. Nottelet, P.; Bataille, L.; Gourgues, G.; Anger, R.; Lartigue, C.; Sirand-Pugnet, P.; Marza, E.; Fronzes, R.; Arfi, Y. The Mycoplasma Surface Proteins MIB and MIP Promote the Dissociation of the Antibody-Antigen Interaction. *Sci Adv* **2021**, 7 (10), eabf2403. https://doi.org/10.1126/sciadv.abf2403.

European Research Council

Dr. Yaser Hashem
Research Director (DR2), Inserm

Yaser Hashem obtained his PhD in 2010 in Strasbourg (France) in computational structural biology where he developed computational approaches for the study of bacterial ribosomal RNA interactions with several antibiotics. After his PhD he went on for a Postdoc at Columbia University in the city of New York with Prof. Joachim Frank (Nobel Laureate for Cryo-EM, 2017) where he worked on understanding the mRNA translation regulation using Cryo-EM and more specifically the translation initiation step in mammals. In 2014, Y. Hashem started his research group in Strasbourg (France) where he became expert in translation regulation in pathogenic parasites and their mammalian hosts. In 2017, Y. Hashem was awarded with the ATIP-Avenir grant, the ERC (European Research Council) starting grant and the "Chair d'Excellence Junior" from the University of Bordeaux and joined the IECB as a Group Leader.

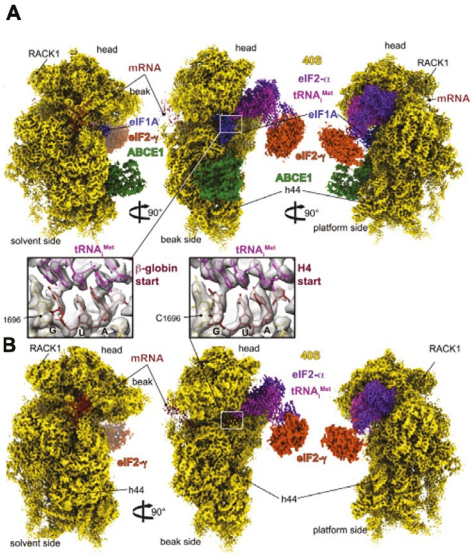
Research team

Dr. Yaser HASHEM Research Director, DR2, (Inserm)
Dr Marie SISSLER, DR2 (CNRS)
Mrs Stéphanie DURRIEU Ai (CNRS)
Dr Ewelina GUCA Postdoc (INSERM)
Dr Aline RIMOLDI RIBEIRO Postdoc (Université de Bordeaux)
Ms Mayara DEL CISTIA PhD student (Université de Bordeaux)
Dr Rajhans Sharma Postdoc (INSERM)
Dr Trung Nguyen Postdoc (INSERM)
Ms Esther Gavello-Fernandez IE (INSERM)
Ms Sramona Barua PhD student (INSERM)

This team is part of the unit "Acides Nucléiques: Régulations Naturelles et Artificielles" (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

RNA Processing and translation regulation in pathogens and hosts (RNA-PT)

The "mRNA translation regulation in pathogens and hosts" group endeavors to study at the molecular level the mRNA translation regulation in several species of pathogens, mainly eukaryotic (both cytosolic and mitochondrial mRNA translation), and their hosts. For several years already, the group has studies existing structural differences in the translation machinery between kinetoplastids and their mammalian hosts in order to discover new and more specific potential therapeutic targets that can be used for the development of safer therapeutic strategies against this family of dangerous parasites. One of the main focuses of the group is the translation initiation step that presents various important structural differences in kinetoplastids, such as Trypanosomes and Leishmanias, when compared to humans. The group is mainly specialized in cryo-electron microscopy, a technique that allows in principle to resolve molecular structures of large sizes to atomic resolutions.



Translation initiation in mammals:

We have solved the structures of two native translation initiation complexes with two archetype abundant cellular mRNAs, the β-globin and histon 4. Our structures are at near-atomic resolution (3.0 to 3.5 Å, respectively, Figure1) and reveal that depending on the mRNA sequence, its interactions with different components of the initiation complex such as eukaruotic initiation factors (eIFs) 1A, 2 and 3 can vary. These complexes can be directly compared with those from several species of pathogenic protozoa.

Figure1. Late-stage 48S initiation complexes (48SIC) from mammals. Thanks to grad-cryo protocol we were able to purify native IC in native conditions. ***A,*** *b-globin IC.* ***B,*** *histon 4 IC. In boxes a blow up on the start-initiation codons for both complexes. From Simonetti & Guca at al. Cell Reports 2020.*

Translation initiation in kinetoplastids:

The initiation stage is expected to represent numerous variations in pathogenic protozoa such as kinetoplastids (like T. *cruzi*, T. *brucei* and L. *major*) compared to its mammalian counterpart because of the presence of several large rRNA expansion segments at the binding site of several initiation factors such as eIF3. Protozoa like kinetoplastids present a complex life cycle where the parasite spends most of its life in an insect vector before being transmitted to a mammalian host upon bitting. Moreover, *in vitro* growth of the parasite reveals various population regulation points aimed at optimizing the environmental resources such as oxygen and carbon resources. Therefore, we first attempted to study their in vitro growth in order to retrieve the best conditions allowing the purification of canonical translation initiation complexes.

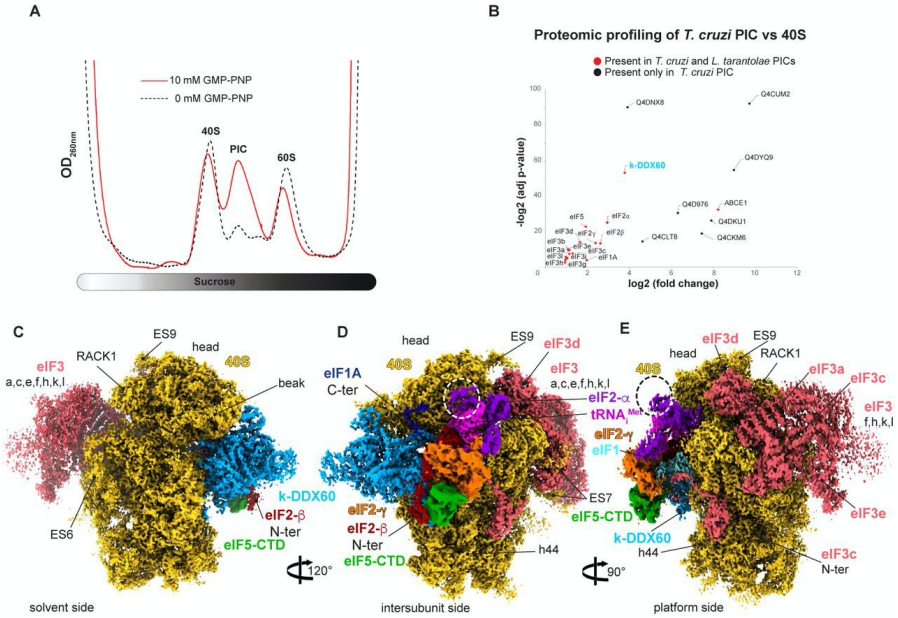


Figure2. Composition and cryo-EM structure of the T. cruzi 43S PIC.
***(A)** The effect of the GMP-PNP treatment on the 43S PIC stabilization in the T.cruzi lysate assessed by UV absorbance profile analyses **(B)** Proteomic profiling of the endogenous pre-initiation complex in comparison with native 40Ss purified from the T. cruzi cell lysate (see methods for the validation). **(C)** The overall structure of the T. cruzi 43S PIC shown from the intersubunit side. The initiation factors are colored variably. **(D)** The 43S PIC recons-truction focused on the solvent side. Extra density of eIF2α corresponding to the kinetoplastidian specific N-terminal insertion is encircled by a dashed line. **(E)** The 43S PIC reconstruction focused on eIF3 and the 40S platform. From Bochler et al. 2020 (Cell Reports).*

The study of the dynamics of growth of epimastigote forms from trypanosoma cruzi and Leishmania tarentolae was carried out. After establishing the best growth conditions for both parasites, we have attempted the purification of initiation complexes using our grad-cryo protocol at different time-points of the growth curves and only at the 3rd growth day we were able to harvest the (pre)initiation complexes in sufficient yield to obtain a cryo-EM structure, the reason of which remains unknown.
The purified complexes were solved by cryo-EM at 3.3Å revealing the presence of several kinetolastids-specific features such as the presence of an additional helicase involved in the initiation process that we have termed DDX60-like because of its faint homology to mammalian DDX60 (Figure2).

Mitochondrial translation regulation: In the past years the team has heavily invested in investigating translation regulation in mitochondria in both pathogens and hosts. Thus, we have recently published the cryo-EM structure of the plant mitoribosome, as plants are also known to be hosts for several species of kinetoplastids (Waltz et al. Nature plants 2019, Waltz & Soufari et al. Nature plants 2020, Figure 3), but also from green algae *Chlamydomonas reinhardtii* (Waltz et Salinas, Nature Comm. 2022) and *T. cruzi* and *L. tarentolae* (Soufari et al. PNAS plants 2020).

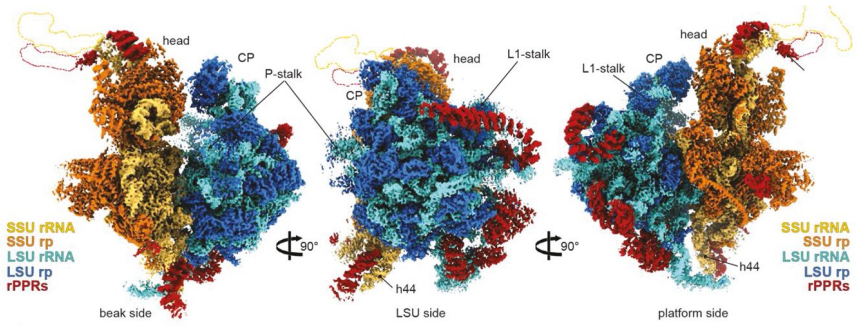


Figure3. Overall structure of the plant mitochondrial ribosome.
rRNAs are colored in light blue (LSU) and yellow (SSU) and ribosomal proteins in blue (LSU) or orange (SSU). A dozen pentatricopeptide repeats proteins (PPR), specific to the plant mitoribosome were discovered and termed ribosomal PPR (rPPR), shown in red. From Waltz & Soufari et al. Nature plants 2020.

Selected publications

1. Waltz, F.; Soufari, H.; Bochler, A.; Giegé, P.; Hashem, Y. Cryo-EM Structure of the RNA-Rich Plant Mitochondrial Ribosome. *Nat. Plants* **2020**, 6 (4), 377-383. https://doi.org/10.1038/s41477-020-0631-5.

2. Sweeney, T. R.; Dhote, V.; Guca, E.; Hellen, C. U. T.; Hashem, Y.; Pestova, T. V. Functional Role and Ribosomal Position of the Unique N-Terminal Region of DHX29, a Factor Required for Initiation on Structured Mammalian MRNAs. *Nucleic Acids Research* **2021**, 49 (22), 12955-12969. https://doi.org/10.1093/nar/gkab1192.

3. Waltz, F.; Salinas-Giegé, T.; Englmeier, R.; Meichel, H.; Soufari, H.; Kuhn, L.; Pfeffer, S.; Förster, F.; Engel, B. D.; Giegé, P.; Drouard, L.; Hashem, Y. How to Build a Ribosome from RNA Fragments in Chlamydomonas Mitochondria. *Nat Commun* **2021**, 12 (1), 7176. https://doi.org/10.1038/s41467-021-27200-z.

4. Sissler, M.; Hashem, Y. Mitoribosome Assembly Comes into View. *Nat Struct Mol Biol* **2021**, 28 (8), 631-633. https://doi.org/10.1038/s41594-021-00640-3.

5. Soufari, H.; Parrot, C.; Kuhn, L.; Waltz, F.; Hashem, Y. Specific Features and Assembly of the Plant Mitochondrial Complex I Revealed by Cryo-EM. *Nat Commun* **2020**, 11 (1), 5195. https://doi.org/10.1038/s41467-020-18814-w.

6. Bochler, A.; Querido, J. B.; Prilepskaja, T.; Soufari, H.; Simonetti, A.; Del Cistia, M. L.; Kuhn, L.; Ribeiro, A. R.; Valášek, L. S.; Hashem, Y. Structural Differences in Translation Initiation between Pathogenic Trypanosomatids and Their Mammalian Hosts. *Cell Reports* **2020**, 33 (12), 108534. https://doi.org/10.1016/j.celrep.2020.108534.

7. Simonetti, A.; Guca, E.; Bochler, A.; Kuhn, L.; Hashem, Y. Structural Insights into the Mammalian Late-Stage Initiation Complexes. *Cell Reports* **2020**, 31 (1), 107497. https://doi.org/10.1016/j.celrep.2020.03.061.

8. Soufari, H.; Waltz, F.; Parrot, C.; Durrieu-Gaillard, S.; Bochler, A.; Kuhn, L.; Sissler, M.; Hashem, Y. Structure of the Mature Kinetoplastids Mitoribosome and Insights into Its Large Subunit Biogenesis. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, *117* (47), 29851-29861. https://doi.org/10.1073/pnas.2011301117.

European Research Council

Dr. Axel Innis
Research Director (DR2), Inserm

Axel Innis did his PhD in structural biology at the University of Cambridge, under the supervision of Prof. Tom Blundell (1998–2002). He then joined the group of Dr. R. Sowdhamini at the National Centre for Biological Sciences in Bangalore as a visiting fellow (2002–2004), where he developed a computational method for identifying functionally important sites in proteins. Following his time in India, Axel joined the group of Prof. Thomas Steitz at Yale University (2004–2012) to work on a little-known form of translational control: gene regulation by nascent polypeptides. He joined IECB and ARNA as a group leader in January 2013, was awarded the 2017 Coups d'Elan Prize for French Research from the Bettencourt-Schueller Foundation and was selected as a 2017 EMBO Young Investigator.

Research team

Dr. Axel INNIS Research Director (DR2), (Inserm)
Dr. Thibaud RENAULT Researcher (CRCN)
Dr. Anne BOURDONCLE Lecturer (MCU) (Univ. Bordeaux)
Dr. Fanny BOISSIER Project engineer (visiting) (Univ. Bordeaux)
Ms. Mélanie GILLARD-BOCQUET Project engineer Inserm – (Univ. Paris Descartes)
Dr. Aitor MANTECA Postdoc (INSERM)
Dr. Thomas PERRY Postdoc (INSERM)
Dr. Anne-Xander VAN DER STEL Postdoc (INSERM)
Ms. Pauline COSSARD PhD student (INSERM)
Ms. Elodie LEROY PhD student (INSERM)
Ms. Anaïs LABECOT M2 Intern (Univ. Bordeaux)

This team is part of the unit "Acides Nucléiques: Régulations Naturelles et Artificielles" (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

Translational Regulation of Gene Expression

Ribosomes are the large macromolecular complexes responsible for accurately translating the genetic information contained in messenger RNA into protein. Our group seeks to understand how ribosomes make proteins, how their activity is regulated in response to different stimuli, and how a variety of small molecules are able to block these complex molecular machines. Our main focus is on the bacterial ribosome and how it is affected by nascent proteins known as arrest peptides, antimicrobial peptides produced by the host immune response, and antibiotics that target the translational machinery (Fig. 1).
In order to determine how the ribosome is regulated at the molecular level, we use a combination of structural biology (cryo-EM), high-throughput functional characterization, biochemistry and computational biology.

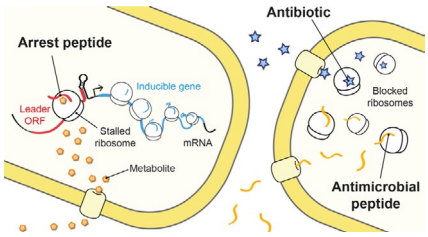


Figure 1 – Different types of molecules studied in the group that target the ribosome

Arrest peptides

During translation, nascent proteins pass through a long cavity spanning the large subunit of the ribosome – known as the nascent polypeptide exit tunnel – before being released into the cytoplasm or delivered to the protein translocation machinery. Although most proteins can easily complete this journey, interactions between specific nascent amino acid sequences and the exit tunnel result in impaired translation and ribosome stalling on the messenger RNA. These arrest peptides often block their own translation in response to a small molecule, such as a drug or metabolite, which is sensed by the ribosome nascent chain complex. Thus, arrest peptides are used for metabolite-dependent gene regulation in both prokaryotes and eukaryotes (Seip & Innis, 2016).
One of the group's main objectives is the large-scale identification and characterization of arrest peptides in bacteria, which we believe constitute a significant fraction of the hidden proteome of bacteria – the collection of short open reading frames (<75 amino acids) that have escaped genome annotation to date. For example, we have recently identified a new arrest peptide in γ-proteobacteria, called SpeFL, and have shown that the capture of a single molecule of the amino acid ornithine by a ribosome translating SpeFL is sufficient to activate polyamine biosynthesis. Using cryo-EM, we have shown that the bacterial ribosome and SpeFL form a highly selective binding pocket for L-ornithine, capable of discriminating between this amino acid and near-cognate ligands (Herrero del Valle et al., 2020). More recently, we have shown how one of the first arrest peptides identified, TnaC, regulates indole production in γ-proteobacteria by detecting a single molecule of the amino acid L-Tryptophan (van der Stel et *al.*, 2021), and how another arrest peptide, ErmDL, controls the expression of methyltransferase conferring resistance to macrolide antibiotics in response to increased concentrations of these drugs (Beckert et *al.*, 2021).
This and earlier studies have also shown that arrest peptides block translation by interfering with key aspects of ribosome function, such as tRNA accommodation, peptide bond formation or peptide release. However, the arrest code that determines whether a given nascent peptide is likely to inhibit its own synthesis remains to be elucidated, the range of metabolites that can be detected by the nascent peptide is unknown, and the molecular basis of metabolite sensing by the ribosome is only just beginning to be understood.
Using cryo-EM and high-throughput tools developed in-house – such as inverse toeprinting (Seip et al., 2018) – we are systematically addressing these questions in order to reveal the true extent of metabolite sensing by arrest peptides.

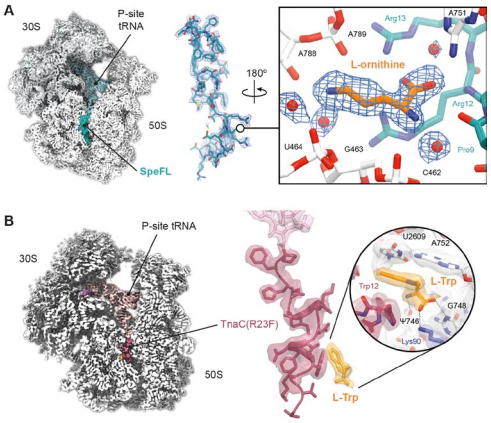


Figure 2 – Structural basis for the recognition of L-ornithine by a SpeFL-70S complex and of L-Trp by a TnaC-70S complex. (A, B) Transverse sections of cryo-EM density maps of the (A) SpeFL-70S (Herrero del Valle et al., 2020) and (B) TnaC-70S complexes (van der Stel et al., 2021), with a focus on the nascent peptides and bound (A) L-ornithine or (B) L-Trp.

Antimicrobial peptides

Proline-rich antimicrobial peptides (PrAMPs) produced by the host immune response of insects and mammals display potent antimicrobial activity against Gram-negative bacteria and therefore represent a promising avenue for antibiotic development.

Although PrAMPs such as oncocin (from the milkweed bug) or bactenecin-7 (from cows) were first thought to inhibit bacterial growth by binding to the chaperone protein DnaK, recent studies have shown that they have much greater affinity for the bacterial ribosome. However, their detailed mode of action remained unclear.

In order to determine how these peptides inhibit translation, we determined the crystal structures of five different PrAMPs in complex with the *Thermus thermophilus* 70S ribosome. Our structures showed that these host defense molecules inhibit the transition from the initiation phase to the elongation phase of translation by binding to the nascent polypeptide exit tunnel and peptidyl transferase center of the ribosome (Seefeldt et al., 2015 and 2016, Mardirossian et al., 2018) (Fig. 3). Since these natural compounds share structural similarities with arrest peptides, the latter may prove helpful in steering the search for new peptide-based antimicrobials that are effective against resistant pathogens.

Using structural biology, droplet-based microfluidics, and biochemistry, we continue to explore the mechanisms by which naturally occurring antimicrobial compounds target and inhibit the bacterial translational machinery (Cytrinska et al. 2020).

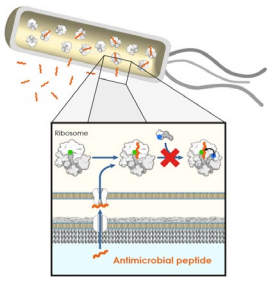


Figure 3 – Ribosome inhibition by antimicrobial peptides. The proline-rich antimicrobial peptides Onc112, Pyrrhocoricin, Metalnikowin, Bac7 and Tur1A inhibit bacterial protein synthesis by blocking and destabilizing the translation initiation complex (Seefeldt et al. 2015, 2016; Mardirossian et al., 2018).

Antibiotics

The threat of bacteria resistant to multiple antibiotics is a major public health challenge that must be tackled through coordinated action on multiple levels. As infectious pathogens have become increasingly resistant to the available drugs, antibiotic discovery programs in major pharmaceutical companies have struggled to produce new antibiotic scaffolds capable of sidestepping current resistance mechanisms. Therefore, new strategies are needed to secure a steady supply of scaffolds and counter the spread of resistance.

The bacterial ribosome is a target for several major classes of antibiotics, including molecules that block peptide bond formation (chloramphenicol, oxazolidinones), impede the synthesis and movement of nascent proteins through the exit tunnel (macrolides), interfere with the decoding of messenger RNA (aminoglycosides) or prevent the translocation of tRNAs during the elongation step of protein synthesis (tuberactinomycins).

Using structural biology and high-throughput approaches, we are (i) characterizing bacterial arrest peptides responsible for the induction of *erm* resistance genes in response to macrolide antibiotics (Beckert et *al.*, 2021), and (ii) revisiting the mechanisms of action of ribosome-targeting antibiotics, focusing on the defined functional states they target. This includes re-examining poorly characterized natural products from the golden age of antibiotic discovery (1950-1960s) to identify the detailed molecular mechanisms by which they block translation. A better understanding of how these antibiotics work could help design improved molecules that are effective against resistant pathogens.

In addition, we are developing high-throughput approaches that use the bacterial ribosome as a platform for the production and selection of translation inhibitors (Charon et *al.*, 2018). We are particularly interested in molecules that target new sites on the ribosome, as they could be used as scaffolds to design novel drugs capable of bypassing known resistance mechanisms.

Selected publications

1. Herrero del Valle, A.; Seip, B.; Cervera-Marzal, I.; Sacheau, G.; Seefeldt, A. C.; Innis, C. A. Ornithine Capture by a Translating Ribosome Controls Bacterial Polyamine Synthesis. *Nat Microbiol* **2020**, 5 (4), 554-561. https://doi.org/10.1038/s41564-020-0669-1.

2. Beckert, B.; Leroy, E. C.; Sothiselvam, S.; Bock, L. V.; Svetlov, M. S.; Graf, M.; Arenz, S.; Abdelshahid, M.; Seip, B.; Grubmüller, H.; Mankin, A. S.; Innis, C. A.; Vázquez-Laslop, N.; Wilson, D. N. Structural and Mechanistic Basis for Translation Inhibition by Macrolide and Ketolide Antibiotics. *Nat Commun* **2021**, 12 (1), 4466. https://doi.org/10.1038/s41467-021-24674-9.

3. Van der Stel, A.-X.; Gordon, E. R.; Sengupta, A.; Martínez, A. K.; Klepacki, D.; Perry, T. N.; Herrero del Valle, A.; Vázquez-Laslop, N.; Sachs, M. S.; Cruz-Vera, L. R.; Innis, C. A. Structural Basis for the Tryptophan Sensitivity of TnaC-Mediated Ribosome Stalling. *Nat Commun* **2021**, 12 (1), 5340. https://doi.org/10.1038/s41467-021-25663-8.

European Research Council

Structural Biology of Biofilms

Dr. Petya Violinova KRASTEVA
Research Scientist (CRCN), CNRS
UMR5248 CBMN

Dr. Petya V. Krasteva joined the CBMN as an IECB group leader in October 2019.
Her research focuses on cyclic dinucleotide signaling and extracellular matrix secretion in bacterial biofilm formation and pathogenesis. Combining X-ray crystallography, biophysical and biochemical assays, cryoelectron microscopy and in cellulo functional studies, her 'Structural Biology of Biofilms' team aims to provide a comprehensive view of bacterial social networks that spans the different resolution levels and present novel anti-infectives.
Petya Krasteva completed her PhD in Molecular and Cell Biology at Ivy League's Cornell University in January 2011, after which she joined the editorial team of Nature Methods at Nature Publishing Group, New York. For her postdoc, she moved to the Institut Pasteur in Paris in 2012 and started her independent team as a CNRS CRCN and an ATIP-Avenir laureate in the end of 2016 at the I2BC, Gif-sur-Yvette.
For her work on bacterial signaling and biofilm formation, Petya Krasteva is the recipient of the Prix Jacques Monod (Fondation de France, 2016), the CNRS Médaille de Bronze (2019) and an ERC Starting Grant (BioMatrix, 2018-2023).

Research team

Dr. Petya V. KRASTEVA CRCN, CBMN (CNRS)
Marion DECOSSAS Research engineer (CNRS)
Dr. Axel SIROY Post-Doc CBMN (CNRS)
Lucia TORRES-SANCHEZ Ph.D. candidate CBMN (CNRS)
Marie JOYEAU Ph.D. candidate CBMN (CNRS)
Wiem ABIDI Ph.D. candidate CBMN (CNRS)
Thibault SANA Research engineer (CNRS)
Nicolas MAURICE L3 Intern CBMN (CNRS)
Sophie MOUGINOT L3 Intern CBMN (CNRS)
Lucie PUYGRENIER L3 Intern and Assistant Engineer CBMN (CNRS)
William NICOLAS PostDoc (CalTech)

This team is part of the unit "Chimie et Biologie des Membranes et des Nano-objets" (CBMN), CNRS UMR5248/INP/Univ. Bordeaux

The Krasteva Lab's research focuses on cyclic dinucleotide signaling and extracellular matrix secretion in bacterial biofilm formation and pathogenesis. Combining X-ray crystallography, biophysical and biochemical assays, cryo-EM and in cellulo functional studies, the 'Structural Biology of Biofilms' (SBB) team aims to provide a comprehensive view of bacterial social networks that spans the different resolution levels and presents molecular blueprints for the development of novel anti-infectives.

Currently the team's research is focused on two main scientific questions: i) what are the intracellular signaling mechanisms that regulate bacterial biofilm formation and, ii) what are the structure, function and dynamics of the membrane-embedded biosynthetic platforms for the secretion of extracellular matrix components.

Most recently, the 'Structural Biology of Biofilms' team provided unprecedented insights into the structural biology of bacterial cellulose secretion (BCS) systems in bacterial biofilms with complete structure-function analyses of a megadalton-sized membrane-embedded Bcs secretion macrocomplex, as well as multiple regulatory subcomplexes (Zouhir et *al.* ***mBio*** 2020 and Abidi et *al.* ***Science Advances*** 2021).

Most bacteria respond to surfaces by the biogenesis of intracellular c-di-GMP that acts at the transcriptional, translational and post-translational levels to inhibit motility and stimulate biofilm formation via secreted adherence factors. Many free-living and pathogenic enterobacteria secrete biofilm-promoting cellulose using a multicomponent, envelope-embedded Bcs secretion system under the control of intracellular second messenger c-di-GMP. The molecular understanding of system assembly and cellulose secretion has been largely limited to the crystallographic studies of a distantly homologous BcsAB synthase tandem and a low-resolution reconstruction of an assembled macrocomplex encompassing most of the inner-membrane and cytosolic Bcs subunits. Using X-ray crystallography and cryo-EM data collected at the Soleil and ESRF synchrotrons, we recently presented the cryo-EM structure of the assembled Bcs macrocomplex, as well as multiple crystallographic snapshots of regulatory subcomplexes. The structural and functional data revealed unexpected subunit stoichiometry, multisite c-di-GMP recognition and ATP-dependent regulation; uncovered the mechanism of asymmetric system assembly and periplasmic crown polymerization; and suggest multilevel control spanning protein expression, folding and membrane targeting among subunits.

Selected publications

1. Altinoglu, I.; Abriat, G.; Carreaux, A.; Torres-Sánchez, L.; Poidevin, M.; Krasteva, P. V.; Yamaichi, Y. Analysis of HubP-Dependent Cell Pole Protein Targeting in Vibrio Cholerae Uncovers Novel Motility Regulators. *PLoS Genet* **2022**, 18 (1), e1009991. https://doi.org/10.1371/journal.pgen.1009991.

2. Abidi, W.; Zouhir, S.; Caleechurn, M.; Roche, S.; Krasteva, P. V. Architecture and Regulation of an Enterobacterial Cellulose Secretion System. *Sci Adv* **2021**, 7 (5), eabd8049. https://doi.org/10.1126/sciadv.abd8049.

3. Zouhir, S.; Abidi, W.; Caleechurn, M.; Krasteva, P. V. Structure and Multitasking of the C-Di-GMP-Sensing Cellulose Secretion Regulator BcsE. *mBio* **2020**, 11 (4), e01303-20. https://doi.org/10.1128/mBio.01303-20.

4. Abidi, W.; Torres-Sánchez, L.; Siroy, A.; Krasteva, P. V. Weaving of Bacterial Cellulose by the Bcs Secretion Systems. FEMS *Microbiol Rev* **2022**, 46 (2), fuab051. https://doi.org/10.1093/femsre/fuab051.

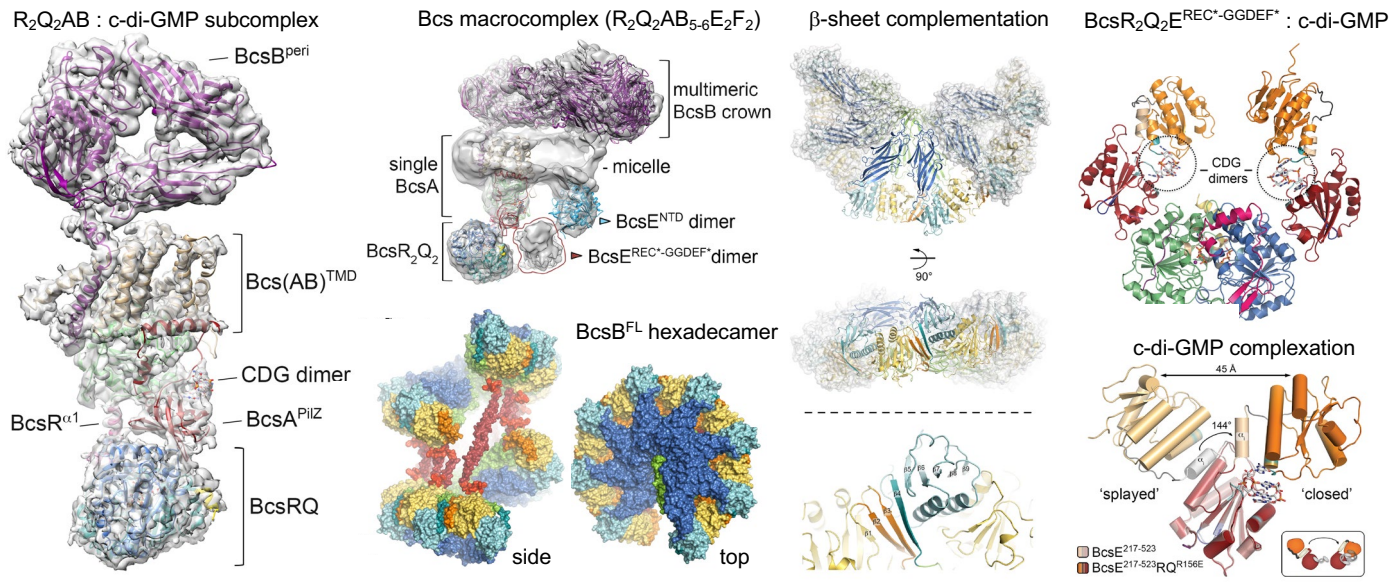


Figure : Atomic-resolution insights in Bcs macrocomplex assembly
From left: cryo-EM structure of the BcsRQAB assembly; cryo-EM structures of the Bcs macrocomplex (top) and homooligomeric BcsBFL (bottom); conserved b-sheet complementation-based BcsB oligomerization; crystal structure of the BcsRQEREC-GGDEF* complex (top) and BcsE conformational changes upon c-di-GMP binding (bottom)*

Dr. Nicolas Reyes
Research Director (DR2),
CNRS/Univ. Bordeaux

My work focuses on the molecular mechanisms of human membrane proteins. I have a multidisciplinary background in membrane protein biophysics spanning from single-molecule electrophysiological measurements (*Nature 2006*; visiting PhD student at The Rockefeller University, USA) to atomic-resolution structure determination (*Nature 2009*; Postdoc at Weill Cornell, USA).
As an early-career independent researcher, my laboratory determined the first 3D structures of an essential synaptic component in the human brain, namely excitatory amino acid transporters, and a first-in-class allosteric inhibition mechanism *(Nature 2017)*.
More recently, we studied receptor *(Science 2020)* and transport *(EMBO J. 2022)* mechanisms of different membrane protein systems with a focus on human solute carriers.
Research in my lab has mainly been funded by international grants including ERC Starting and Consolidator grants.

Research team

Dr. Nicolas REYES Research Director, DR2 (CNRS)
Dr. Juan CANUL-TEC Postdoc (CNRS)
Dr. Kapil GOUTAM Postdoc (CNRS)
Dr. Miryam VILLALBA Postdoc (Univ. Bordeaux)
Dr. Emmanuel Nji Postdoc (Univ. Bordeaux)
Shashank KHARE PhD Student (Univ. Bordeaux)

This team is part of the unit: "Fundamental microbiology and pathogenicity" (MFP), CNRS UMR5234/Univ. Bordeaux

Membrane Protein Mechanisms

Human solute carriers (hSLC) form a superfamily of integral membrane proteins that transport essential molecules and ions across membranes, and are the cellular receptors of human and pathogenic proteins. Their transport and receptor functions are involved in a wide range of pathological conditions, making hSLCs important emerging drug targets in neurodegeneration, cancer, and infectious diseases, among others.
Our research program aims to unravel novel transport, receptor and pharmacological mechanisms of medically important hSLCs using a multidisciplinary biophysical approach. To achieve this, we combined high-resolution cryo-electron microscopy with functional approaches to probe hSLC complexes' structures, dynamics, and thermodynamics.

Human excitatory amino acid transporters (EAATs) maintain glutamate gradients in the brain essential to neurotransmission and to prevent neuronal death. They use ionic gradients as energy source, and co-transport transmitter into the cytoplasm with Na+ and H+, while countertransport K+ to re-initiate the transport cycle. However, the molecular mechanisms underlying ion-coupled transport remain incompletely understood. During the reporting period, we determined 3D structures and studied the binding thermodynamics of EAAT1 in different ionic conditions, including elusive counter-transport ion bound states. Binding energies of Na+ and H+, and unexpectedly Ca2+, are coupled to neurotransmitter binding. Ca2+ competes for a conserved Na+ site suggesting a regulatory role of Ca2+ in glutamate transport at the synapse, while H+ binds to a conserved glutamate residue stabilizing substrate occlusion. The countertransported ion binding site overlaps with that of glutamate, revealing the K+ mechanism to exclude the transmitter during the transport cycle, and to prevent its neurotoxic release on the extracellular side (Fig. 1).
In the proposed mechanism, Na+ binding to Na1-Na3 and protonation of E406386 are thermodynamically coupled to transmitter binding and occlusion, and lead to the formation of the transmitter translocation complex, represented by EAAT1CRYST Na+/transmitter bound crystal structure (Fig. 2). In turn, K+ binding to KCT promotes self-occlusion, and formation of a K+ translocation complex that excludes the transmitter, and it is represented by EAAT1WT cryo-EM structure (Fig. 3).
Our findings shed light on controversial and important aspects of EAATs transport cycle, and suggest novel mechanisms to regulate glutamate levels at tripartite synapses.

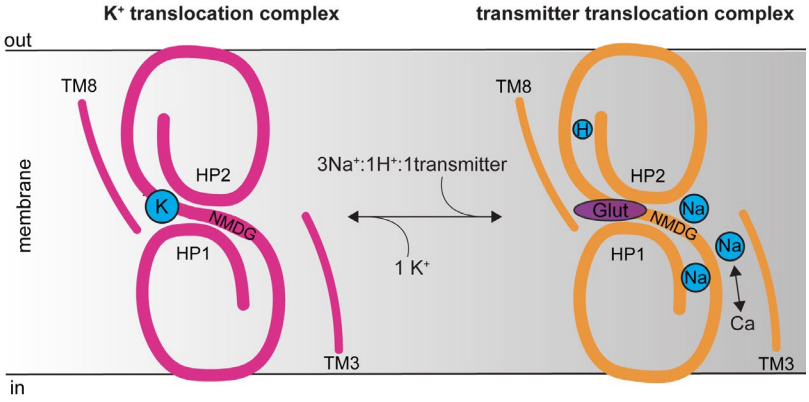


Figure 1 EAAT1 ion-coupled transport mechanism
Cartoon representation of Na+/H+/transmitter, and K+ translocation complexes, respectively.

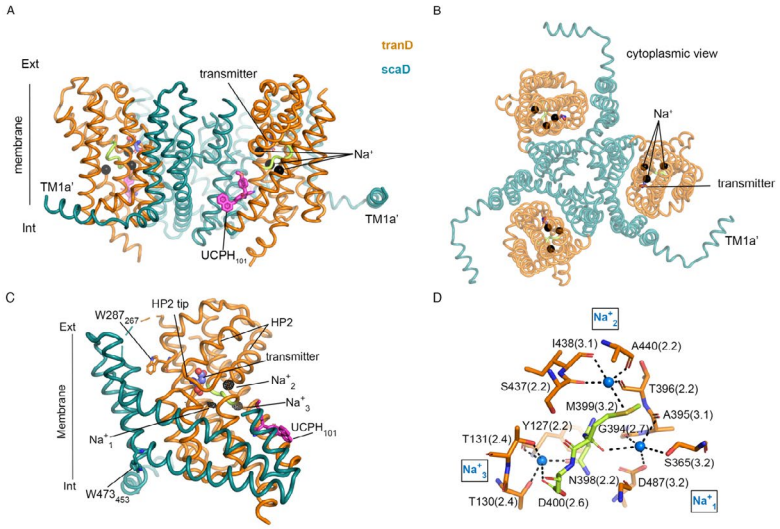


Figure 2 EAAT1CRYST Na+/transmitter bound structure
A, B. Views of EAAT1CRYST trimer in outward-facing Na+/transmitter-bound state, including N-term helix TM1a'. C. EAAT1CRYST protomer viewed from the membrane with tranD orange, scaD teel (TM4a,b omitted), and 398NMDG motif green. Fo-Fc Na+-omit map contoured at 3.5σ (black mesh) around the tranD core. D. Coordination details of three Na+-bound (blue sphere) to EAAT1CRYST. Residue numbering corresponds to EAAT1WT, and the coordination distance (angstrom) is in parenthesis.

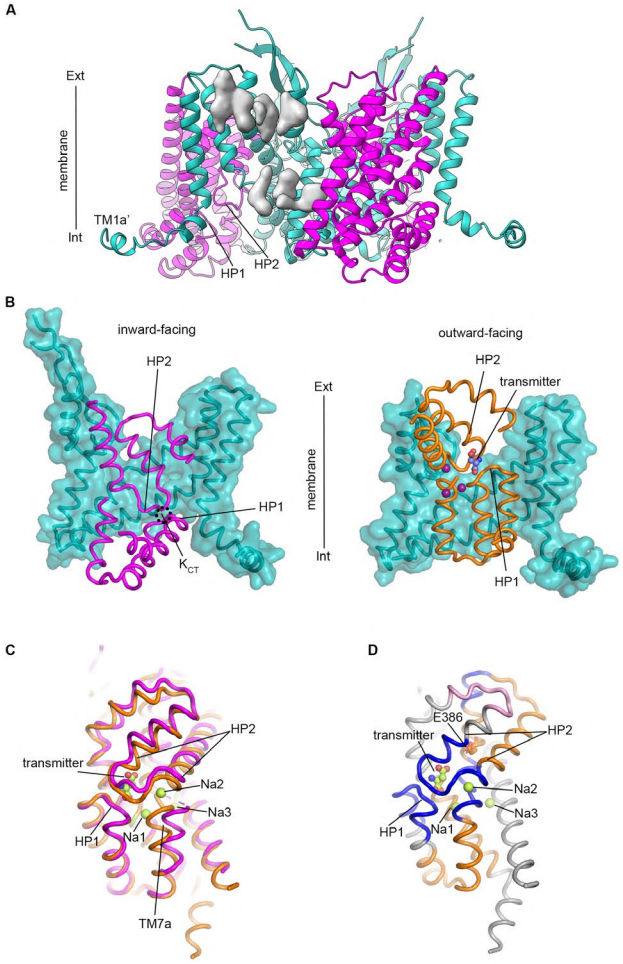


Figure 3 CryoEM structure and HDX-MS changes in K+ buffer
A. CryoEM structure of EAAT1WT trimer with tranDs and scaDs depicted in magenta and teal, respectively. Non-protein extra density corresponding to lipid/detergent molecules is depicted in grey. B. Comparison of EAAT1WT (left) and EAAT1CRYST (right) structures in inward- and outward-facing states, respectively. Several TMs were removed for clarity. C. TranDs from EAAT1WT (magenta) and EAAT1CRYST (orange) structures are overlapped using HP1 as reference. D. K+-induced HDX increase (blue) and decrease (pink) in EAAT1CRYST is mapped on Na+/transmitter-bound tranD structure. Unchanged regions (orange) and those outside HDX-MS sequence coverage (grey) are also shown.

Selected publications

1. Kumar, A.; Planchais, C.; Fronzes, R.; Mouquet, H.; Reyes, N. Binding Mechanisms of Therapeutic Antibodies to Human CD20. *Science* **2020**, 369 (6505), 793-799. https://doi.org/10.1126/science.abb8008.

2. Canul-Tec, J. C.; Kumar, A.; Dhenin, J.; Assal, R.; Legrand, P.; Rey, M.; Chamot-Rooke, J.; Reyes, N. The Ion-coupling Mechanism of Human Excitatory Amino Acid Transporters. *The EMBO Journal* **2022**, 41 (1). https://doi.org/10.15252/embj.2021108341.

atip-avenir

Dr. Frédéric Friscourt
Associate Professor, ATIP-Avenir Fellow, Univ. Bordeaux

Frédéric Friscourt received his PhD from the University of Glasgow, UK in 2009, under the guidance of Prof. P. Kočovský, on the development of novel chiral ligands for enantioselective catalysis. He then joined the group of Prof. G-J. Boons at the Complex Carbohydrate Research Center, GA, USA, as a post-doctoral research associate (2009-2014) in order to transition to chemical biology research. There, he became involved in the design of probes for imaging the glycome. In 2014, he obtained a Junior Chair of Excellence from the University of Bordeaux and was soon after recruited as a group leader at the IECB in Bordeaux. He received the prestigious CNRS-ATIP-Avenir award (2017) and was recently promoted to Associate Professor in Chemical Biology at the University of Bordeaux, France (2021). His current research focuses on using organic chemistry to develop novel tools that can probe and control the influence of mammalian glycans physiologically and pathologically.

Research team

Dr. Frédéric FRISCOURT Associate Professor, ATIP-Avenir Fellow (Univ. Bordeaux)
Dr. Jürgen SCHULZ IR2 (CNRS)
Dr. Zoeisha CHINOY PostDoc (Univ. Bordeaux)
Khalaf TAREK PhD Student (Univ. Bordeaux)
Léna Atlan Engineering student I2 (Univ. Rennes)
Emma Urrère Undergraduate student BTS (Lycée St Louis, Bordeaux)

This team is part of the unit "Institut des Sciences Moléculaires" (ISM), CNRS UMR5255/ Univ. Bordeaux

Chemical Neuroglycobiology

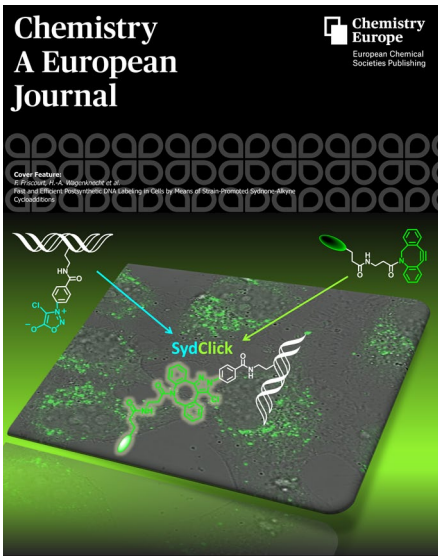
Glycans are chains of monosaccharides that are covalently linked to cell surface proteins and lipids. They have been recognized as key participants in a variety of physiological processes, including angiogenesis, fertilization, cell adhesion and host-pathogen interactions. From a pathological point of view, changes in the glycome of cells are associated with developmental disorders, can mark the onset of cancer and inflammation. Despite these intriguing observations, the molecular mechanisms by which these complex carbohydrates influence cell functions are not well understood due to a lack of suitable biochemical methods. We aim at unravelling the functional roles of mammalian glycans by exploiting organic chemistry to develop novel tools that can probe them in living systems.

Imaging glycans: a daunting task.

Although protein tracking in living cells has become routine experiments in cell biology laboratories thanks to the utilization of genetic reporters, glycans are, unfortunately, not amenable to these imaging techniques, as they are not directly encoded in the genome. As an emerging alternative, the **bioorthogonal chemical reporter strategy**, which elegantly combines the use of metabolically labeled azido sugars and highly reactive cyclooctyne probes, through strain-promoted alkyne azide cycloadditions (SPAAC), is a versatile technology for labeling and visualizing glycans. However, the biological stability of current chemical reporters is not always up to par.
To address these difficulties, we are developing novel chemical reporters with enhanced biological stability while maintaining high reactivity towards cyclooctyne probes.

Sydnones as novel bioorthogonal chemical reporters.

To circumvent the stability issue of azides, we recently developed modified **sydnones**, highly stable aromatic mesoionic 1,3-dipoles, and employed them as chemical reporters for the challenging detection of modified-proteins in complex cellular extracts (*J. Org. Chem.* **2018**, 83, 2058) as well as for the labeling of complex glycans in living cells (*Angew.* Chem. Int. Ed. **2019**, 58, 4281).
In a fruitful collaboration with Prof. H-A. Wagenknecht from the Karlsruhe Institute of Technology, Germany, we recently extended the scope of biomolecules that could be labeled via strain-promoted sydnone-alkyne cycloaddition (SPSAC), to nucleic acids. In this work, sydnone reporters could efficiently be chemically introduced into either 2'-deoxyuridines or 7-deaza-2'-deoxyadenosines. These modified nucleosides were then incorporated into single-stranded DNAs, allowing for their fast postsynthetic labeling with cyclooctyne probes both in vitro and in cells (Chem. Eur. J. **2021**, 27, 16093).



Impact of chemical reporters on the activity of glycan-processing enzymes.

We recently showed that while sydnones could be employed for **tagging complex sialoglycans in living mammalian cells,** their positioning on the sialic acid residue had a strong influence on sialyltransferases substrate recognition (Angew. Chem. Int. Ed. **2019**, 58, 4281) (Figure 1).

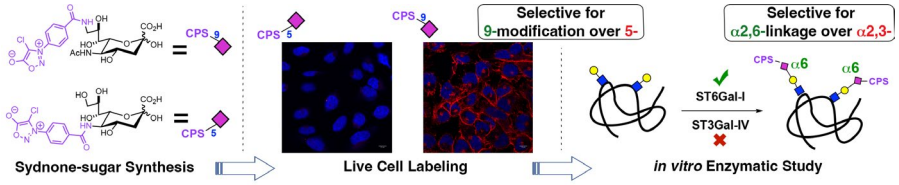


Figure 1. The presence of a sydnone reporter on sialic acid residues affect their biosynthetic processing and consequently is selectively incorporated into specific classes of glycans.

Accordingly, we decided to investigate whether other glycan-processing enzymes would also be affected by the presence of chemical reporters.

We focus our attention on studying the activity of **bacterial sialidases**, enzymes expressed by bacteria during pathogenesis for cleaving sialic acid sugars from mammalian cell-surface glycans in order to adhere and infect the host.

By employing a multidisciplinary approach, including chemo-enzymatic synthesis for generating the unnatural sugars, enzymatic assays for probing in vitro the sialidase activity, cell imaging for visualizing glycans in living cells, and in *silico* modelling for rationalizing the observed molecular effects, we recently identified that pathogenic bacterial sialidases were unable to cleave sialosides displaying a sydnone at the 5-position of sialic acids *in vitro* as well as in living cells (ACS Chem. Biol. **2021**, 16, 2307) (Figure 2). We are currently studying the potential use of this novel strategy for protecting mammalian cells against bacterial invasion.

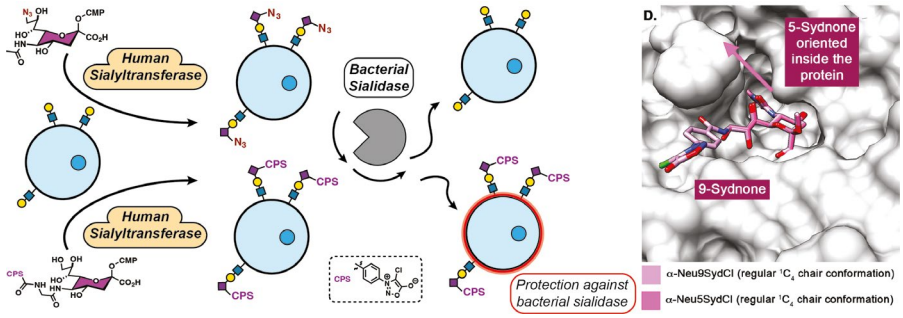


Figure 2. Glyco-edited mammalian cells with azide- or sydnone-modified sialic acids are not recognized similarly by bacterial sialidases and consequently exhibit different level of protecting effects against them. D. Sydnone-modified sialic acids modeled into the active site of C. perfringens sialidase.

Selected publications

1. Chinoy, Z. S.; Friscourt, F. Bioorthogonal Chemical Ligations Towards Neoglycoproteins. *In Comprehensive Glycoscience*; Elsevier, 2021; pp 660-675. https://doi.org/10.1016/B978-0-12-819475-1.00080-8.

2. Friscourt, F., In Science of Synthesis: Click Chemistry, Rutjes, F. P. J. T., Ed.; *Thieme: Stuttgart,* **2021**; p 641-659. https://doi.org/10.1055/sos-SD-235-00329

3. Krell, K.; Pfeuffer, B.; Rönicke, F.; Chinoy, Z. S.; Favre, C.; Friscourt, F.; Wagenknecht, H. Fast and Efficient Postsynthetic DNA Labeling in Cells by Means of Strain-Promoted Sydnone-Alkyne Cycloadditions. *Chem. Eur. J.* **2021**, 27 (65), 16093-16097. https://doi.org/10.1002/chem.202103026.

4. Chinoy, Z. S.; Montembault, E.; Moremen, K. W.; Royou, A.; Friscourt, F. Impacting Bacterial Sialidase Activity by Incorporating Bioorthogonal Chemical Reporters onto Mammalian Cell-Surface Sialosides. *ACS Chem. Biol.* **2021**, 16 (11), 2307-2314. https://doi.org/10.1021/acschembio.1c00469.

Dr. Gilles Guichard
Research Director (DR1), CNRS

Gilles Guichard graduated in chemistry from the Ecole Nationale Supérieure de Chimie in Toulouse (1991) and Univ. Montpellier (1992) in France. He received his PhD from the Univ. Strasbourg (1996) in the field of peptide science. Following post-doctoral research with Prof. Dieter Seebach at the ETH in Zürich (1997) working on the synthesis of β-amino acids and β-peptides, he joined the Institut de Biologie Moléculaire et Cellulaire (IBMC) in Strasbourg as a CNRS Chargé de Recherche (1998). Since 2006, he has been a CNRS Research Director. In 2009, he moved to Bordeaux and joined the Institut de Chimie et Biologie des Membranes et Nanoobjets (CBMN) and the Institut Européen de Chimie et Biologie (IECB). In 2019, he received the Grammaticakis-Neuman award from the Académie des Sciences for his work on foldamers and has been a member of the advisory board of Peptide Science since 2022. His research focuses on the biomimetic chemistry of peptides.

Research team

Dr. Gilles GUICHARD DR1 (CNRS)
Dr. Christel DOLAIN MCU (Univ. Bordeaux)
Dr. Morgane PASCO CRCN
Dr. Guillaume COMPAIN MCU (Univ. Bordeaux)
Dr. Sung HYUN YOO Postdoctoral fellow (Univ. Bordeaux)
Dr. Bo LI Postdoctoral fellow (CNRS)
Dr. Santu BERA Postdoctoral fellow (Univ. Bordeaux)
Dr. Sandeep Mummadi Postdoctoral fellow (CNRS)
Clément MONSARRAT PhD student (Univ. Bordeaux)
Antoine HACIHASANOGLU PhD student (Univ. Bordeaux)
Maxime NEUVILLE PhD student (Univ. Bordeaux)
Aline DELAMARE PhD student (Univ. Bordeaux)
Matthieu BOURGEAIS PhD student (Univ. Bordeaux)
Claire SARAGAGLIA PhD student (Univ. Bordeaux)

This team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS – Université de Bordeaux – Bordeaux INP (UMR 5248)

Peptidomimetic Chemistry

We are interested in designing and elaborating synthetic molecular systems with protein like structure and functions and to investigate their biological and biomedical applications. Although centered on chemical synthesis, our research program is based on a multidisciplinary approach involving spectroscopic studies, crystallographic analyses, combinatorial techniques, and binding studies. NMR and X-ray crystallography have played a major role in the advancement of our research, allowing atomic description and facilitating the design of foldamer-based protein mimics and nanostructures. In recent years, our group has also gained interest in foldamer-based catalysis and in the structure-guided design of peptidomimetics and foldamers as inhibitors of protein-protein interactions with a focus on cancer-related and bacterial targets.

Our main line of research focuses on Peptidomimetic & Foldamer Chemistry with a current focus on the development of functional foldamers. The finding that oligourea foldamers can be interfaced with natural peptide helices (see *Angew Chem Int Ed* 2015) gave impetus for future applications of urea-based foldamers in biology. Recently developed applications include the design of α-helix mimics for inhibiting protein-protein interactions (PPIs) with a focus on cancer-related targets (*Angew Chem Int* Ed 2021 and *Sci Adv* 2021, **Highlight #1**). We have also reported the design of cationic amphiphilic oligourea sequences for delivering nucleic acids into cells (Chem Commun 2021). We also have a continued interest in the use of foldamers to create self-assembled nanostructures that can mimic protein quaternary structures (*Chem Commun* 2021b, **Highlight #2**) Besides our work on foldamers, we are engaged in two programs dedicated to the design of antibacterial compounds that specifically block protein synthesis and DNA replication in bacteria via inactivation of the corresponding molecular machineries: (i) the bacterial ribosome (coll. A. Innis, IECB, Pessac) and (ii) the bacterial sliding clamp (coll. D. Burnouf, IBMC, Strasbourg, see *J Med Chem* 2021, **Highlight #3**).

RECENT HIGHLIGHTS:

Highlight #1: Oligourea-peptide hybrids as inhibitors of protein-protein interactions *(Sci Adv 2021 & Angew Chem Int Ed 2021 &- selected as a hot paper and for a press release)*

Interfacing oligoureas with peptides was used for the first time in this project to design peptide-oligourea hybrids that disrupt PPIs. Following careful optimization of oligourea inserts, we have obtained good binders to ubiquitin ligase MDM2, vitamin D receptor (VDR) and histone chaperone ASF1 (Fig. 1) as well an ensemble of X-ray structures of foldamer ligands bound to their respective target proteins. This strategy, whereby an α-helical segment is replaced by a foldamer insert, may yield peptide analogues with substantial resistance to proteolytic degradation, a feature which is often desirable when developing peptide therapeutics.

Highlight #2: Self-assembly of a urea-based foldamer into helix bundles of multiple stoichiometries *(Chem Comm 2021, selected for cover)*

We have previously reported the strong propensity of amphiphilic aliphatic oligourea foldamers to self-assemble into protein-like architectures in aqueous conditions. In particular, we have described a six-helix bundle formed by the self-assembly of a zwitterionic oligourea foldamer. In continuation of this work we have studied an analogue of this foldamer sequence able to self-assemble in aqueous conditions into helix bundles of multiple stoichiometries. Importantly, we have been able to determine crystal structures of several of these stoichiometries, providing high-resolution snapshots of the structural polymorphism of this foldamer.

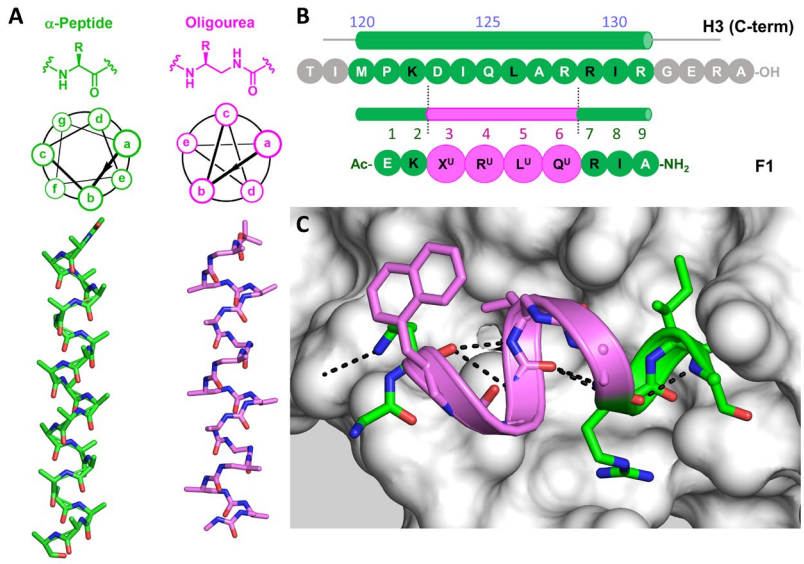


*Fig. 1. (A) Similarities between α-helical and oligourea backbones; (B) Sequence of a foldamer-peptide binder (F1) to ASF1 and comparison with histone H3 C-terminus; (C) crystal structure of **F1** in complex with ASF1 (coll. Françoise Ochsenbein, I2BC).*

Highlight #3: Synthesis and optimization of high affinity peptide binders to the bacterial sliding clamp *(J Med Chem 2021)*

The bacterial DNA sliding clamp (SC) is a promising target for the development of novel antibiotics. In this work we report a structure−activity relationship study of a new series of peptides interacting within the *Escherichia* coli SC (EcSC) binding pocket. Multiple modifications were explored including N-alkylation of the peptide bonds, extension of the N-terminal moiety, and introduction of hydrophobic and constrained residues at the C-terminus. Combinations of several such modifications yielded in several cases to a substantially increased affinity (KD in the range of 30−80 nM) compared to the cognate peptides (Fig. 2). X-ray structure analysis of peptide/EcSC co-crystals revealed new interactions at the peptide−protein interface that can account for the improved binding. Several compounds among the best binders were found to be more effective in inhibiting SC-dependent DNA synthesis.

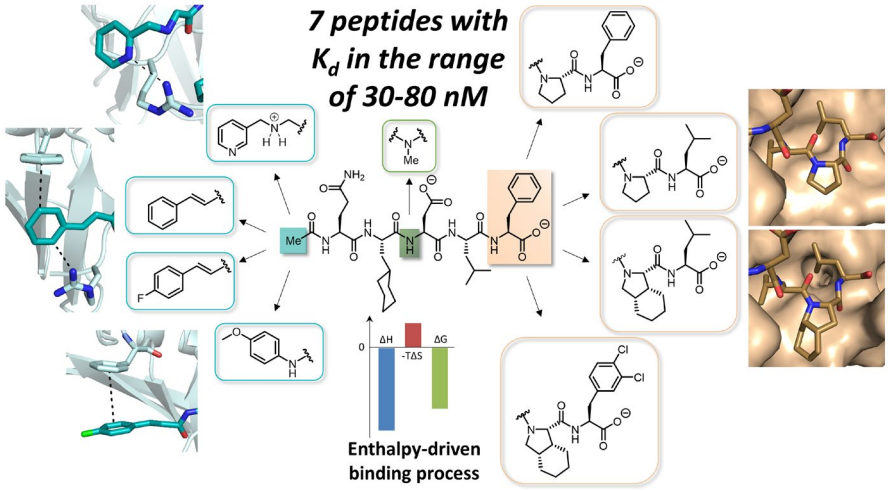


Fig. 2. Discovery of high affinity peptide binders to E. coli sliding clamp (EcSC)

Selected publications

1. Zaky, M. S.; Wirotius, A.-L.; Coulembier, O.; Guichard, G.; Taton, D. A Chiral Thiourea and a Phosphazene for Fast and Stereoselective Organocatalytic Ring-Opening-Polymerization of Racemic Lactide. *Chem. Commun.* **2021**, 57 (31), 3777-3780. https://doi.org/10.1039/D0CC08022E.

2. Collie, G. W.; Lombardo, C. M.; Yoo, S. H.; Pułka-Ziach, K.; Gabelica, V.; Mackereth, C. D.; Rosu, F.; Guichard, G. Crystal Structures Capture Multiple Stoichiometric States of an Aqueous Self-Assembling Oligourea Foldamer. *Chem. Commun.* **2021**, 57 (75), 9514-9517. https://doi.org/10.1039/D1CC03604A.

3. Bornerie, M.; Brion, A.; Guichard, G.; Kichler, A.; Douat, C. Delivery of SiRNA by Tailored Cell-Penetrating Urea-Based Foldamers. *Chem. Commun.* **2021**, 57 (12), 1458-1461. https://doi.org/10.1039/D0CC06285E.

4. Monsarrat, C.; Compain, G.; André, C.; Engilberge, S.; Martiel, I.; Oliéric, V.; Wolff, P.; Brillet, K.; Landolfo, M.; Silva da Veiga, C.; Wagner, J.; Guichard, G.; Burnouf, D. Y. Iterative Structure-Based Optimization of Short Peptides Targeting the Bacterial Sliding Clamp. *J. Med. Chem.* **2021**, 64 (23), 17063-17078. https://doi.org/10.1021/acs.jmedchem.1c00918.

5. Mbianda, J.; Bakail, M.; André, C.; Moal, G.; Perrin, M. E.; Pinna, G.; Guerois, R.; Becher, F.; Legrand, P.; Traoré, S.; Douat, C.; Guichard, G.; Ochsenbein, F. Optimal Anchoring of a Foldamer Inhibitor of ASF1 Histone Chaperone through Backbone Plasticity. *Sci. Adv.* **2021**, 7 (12), eabd9153. https://doi.org/10.1126/sciadv.abd9153.

6. Cussol, L.; Mauran-Ambrosino, L.; Buratto, J.; Belorusova, A. Y.; Neuville, M.; Osz, J.; Fribourg, S.; Fremaux, J.; Dolain, C.; Goudreau, S. R.; Rochel, N.; Guichard, G. Structural Basis for A-Helix Mimicry and Inhibition of Protein-Protein Interactions with Oligourea Foldamers. *Angew. Chem. Int. Ed.* **2021**, 60 (5), 2296-2303. https://doi.org/10.1002/anie.202008992.

7. Yoo, S. H.; Li, B.; Dolain, C.; Pasco, M.; Guichard, G. Urea Based Foldamers. In *Methods in Enzymology*; Elsevier, 2021; Vol. 656, pp 59-92. https://doi.org/10.1016/bs.mie.2021.04.019.

Dr. Emmanuelle THINON
Research scientist (CRCN), CNRS

Emmanuelle Thinon completed her PhD in Chemical Biology at Imperial College London in 2014, under the supervision of Prof. Ed Tate. For her postdoc, thanks to a Marie Skłodowska-Curie Global fellowship, she worked at the Rockefeller University (USA) with Prof. Howard Hang and The Francis Crick Institute (UK) with Dr. Sharon Tooze. In 2019, she was recruited as a research associate (chargé de recherche, CRCN) within the French National Centre for Scientific Research (CNRS), to join the CBMN (Institute of Chemistry & Biology of Membranes & Nanoobjects) in Bordeaux. In November 2019, she joined IECB as a group leader.

Research team

Dr. Emmanuelle THINON Research scientist CRCN, (CNRS)
Chloé Freyermuth PhD student (CNRS)
Loris VERRON Research Engineer (UB)
Dr. Elena CESAR-RODO Postdoc (UB)
Oriane Dietre M2 student (UB)
Yanis Yahiaoui M2 student (UB)
Gaëtan Pignatta M1 student (UB)

This team is part of the unit "Chimie des membranes et des nanoobjets" (CBMN), CNRS UMR5248/INP/ Univ. Bordeaux

Chemical Biology of membrane proteins

The study of small transmembrane proteins can often be challenging. In particular, it can be difficult to tag these proteins with a fluorophore in cellulo without perturbing the proteins localization and function, or to extract and purify them from membranes, without disturbing their structure or interactions with other proteins, for structure determination or for mass spectrometry interaction proteomics. Additionally, these proteins can be post-translationally modified by lipids, but proteomics methods to precisely identify and quantify some of these modifications are noticeably lacking. The "Chemical Biology of membrane proteins group" endeavours to develop and/or apply a combination of chemical and biological approaches to facilitate the study of these small membrane proteins.

The first aim of our work is to use a combination of chemical approaches (site-specific chemical labelling, crosslinking interaction proteomics, chemical proteomics, genetic code expansion, solid state NMR) to characterize small transmembrane proteins involved in viral infections. Some of these proteins are post-translationally modified by S-palmitoylation, which corresponds to the reversible addition of a C16 fatty acid to Cys, often adjacent to the protein transmembrane domain. S-palmitoylation is essential for protein localization and regulation, but its precise function, notably during viral infection, remains unknown for some proteins.
Using a combination of methods, we are currently characterising a small protein involved in viral infections by studying the role and regulation of its S-palmitoylation, its structure in interaction with membranes and by identifying its interaction partners. These studies will help us to understand if this protein could be new antiviral drug target.

The second aim of our work is to develop new methods to tag proteins at the endogenous level (no overexpression). The addition of a tag to a protein, such as GFP (Green Fluorescence Protein) for immunofluorescence studies, can sometimes perturb the protein biophysical properties, localization and/or function. The tag is often added by overexpressing the protein of interest, which can sometimes lead to toxicity, hence the development of new methods to tag proteins at the endogenous level is essential. The tag could be a small fluorophore (BODIPY etc) for live cell imaging studies or with a crosslinking moiety to enable the identification of the interactome of the protein of interest by mass spectrometry-based proteomics. These new methods will be applied to facilitate the study of small membrane proteins.

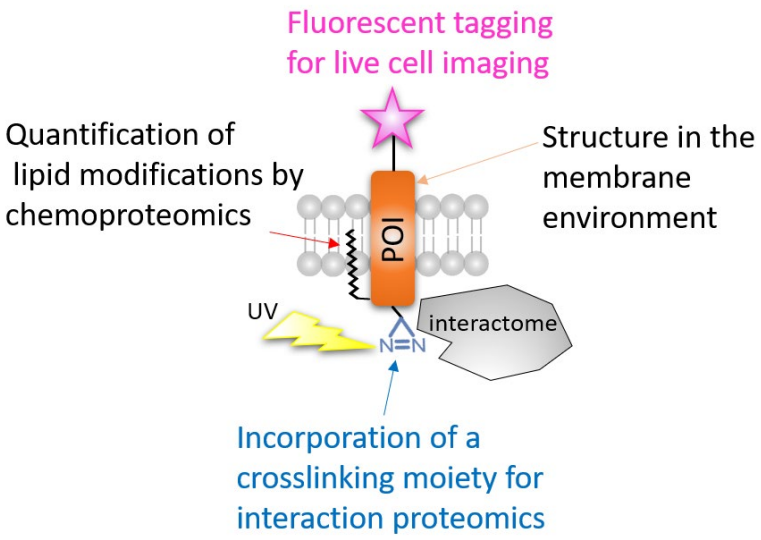


Figure 1. Characterization of small membrane proteins using a combination of chemical and biological methods.

Selected publications

1. Tapodi, A.; Clemens, D. M.; Uwineza, A.; Jarrin, M.; Goldberg, M. W.; Thinon, E.; Heal, W. P.; Tate, E. W.; Nemeth-Cahalan, K.; Vorontsova, I.; Hall, J. E.; Quinlan, R. A. BFSP1 C-Terminal Domains Released by Post-Translational Processing Events Can Alter Significantly the Calcium Regulation of AQP0 Water Permeability. *Exp Eye Res* **2019**, 185, 107585. https://doi.org/10.1016/j.exer.2019.02.001.

2. Thinon, E.; Hang, H. C. Chemical Proteomic Analysis of S-Fatty Acylated Proteins and Their Modification Sites. *Methods Mol Biol* **2019**, 2009, 45-57. https://doi.org/10.1007/978-1-4939-9532-5_4.

3. Spence, J. S.; He, R.; Hoffmann, H.-H.; Das, T.; Thinon, E.; Rice, C. M.; Peng, T.; Chandran, K.; Hang, H. C. IFITM3 Directly Engages and Shuttles Incoming Virus Particles to Lysosomes. *Nat Chem Biol* **2019**, 15 (3), 259-268. https://doi.org/10.1038/s41589-018-0213-2..

Dr. Mikayel AZNAURYAN,
Research scientist (CRCN), Inserm

Mikayel Aznauryan obtained his PhD from Yerevan State University in Armenia (2008–2011). Then, he moved to Switzerland (2012–2014) as a postdoctoral researcher at the Department of Biochemistry of the University of Zurich (Group of Prof. B. Schuler), to work on protein folding and dynamics with single-molecule FRET spectroscopy. Afterwards, Mikayel Aznauryan did a second postdoc (2014–2018) at the Department of Chemistry and the Interdisciplinary Nanoscience Center of Aarhus University in Denmark, where he used single-molecule methods to study the dynamics of nucleic acid structures.
Mikayel Aznauryan has joined IECB at the end of 2018 and has been awarded FRM Jeune equipe and IdEx Chaire Junior grants to start his group. Shortly after, he obtained INSERM researcher position (CRCN) within ARNA laboratory.

Research team

Dr. Mikayel AZNAURYAN Research scientist CRCN (Inserm)
Dr. Carmelo DI PRIMO Research scientist CRHC (Inserm)
Mme. Sabrina ROUSSEAU Engineer, IE (Inserm)
Dr. Laurent FERNANDEZ Postdoc (Inserm)
Dr. Bikash Chandra SWAIN Postdoc (Inserm)
M^me^ Pascale SARKIS PhD student (Univ. Bordeaux)
M^me^ Ani MELTONYAN Technician (Univ. Bordeaux)
M^me^ Valentine AHO M2 intern student (Univ. Bordeaux)
M^me^ Nejma RABHI M1 intern student (Univ. Bordeaux)

This team is part of the unit “Acides Nucléiques: Régulations Naturelles et Artificielles” (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

Single-molecule Biophysics

Intrinsically disordered proteins (IDPs) or proteins containing intrinsically disordered regions (IDRs) are ubiquitous in eukaryotic proteome. They typically lack persistent structure in their native form and do not necessarily require defined structure for molecular recognition and specific function. They are frequently involved in liquid-liquid phase separation (LLPS) driven assembly of various cellular condensates. We use a large variety of biochemical and biophysical tools, among which particularly single-molecule FRET spectroscopy, in order to understand the mechanisms of IDP interactions and to reveal the basis of specificity for molecular recognition and particular function of IDPs, as well as uncover how certain IDP interactions define and modulate the LLPS and formation of cellular condensates.

The key expertise of the group is centered on *in vitro* and in-cell single-molecule FRET spectroscopy, which is our main tool to look at IDPs and their interaction. For this purpose, we also use a variety of other state-of-the-art biochemical and biophysical techniques, such as biomolecular nuclear magnetic resonance (NMR) spectroscopy, surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), live-cell imaging and others, to obtain a comprehensive picture of mechanisms of IDP interactions and to reveal the basis of specificity for molecular recognition and particular function of IDPs.

Currently, in the group we are working on the following research projects:

- investigation of eukaryotic translation initiation and especially the role of disordered translation initiation factors in this process;
- understanding the molecular mechanisms of function of disordered RNA-binding proteins in LLPS and cellular condensates;
- measuring biomolecular binding kinetics, including ternary complexes, fragile targets, strong non-specific binding, thanks to original methodological developments in SPR.

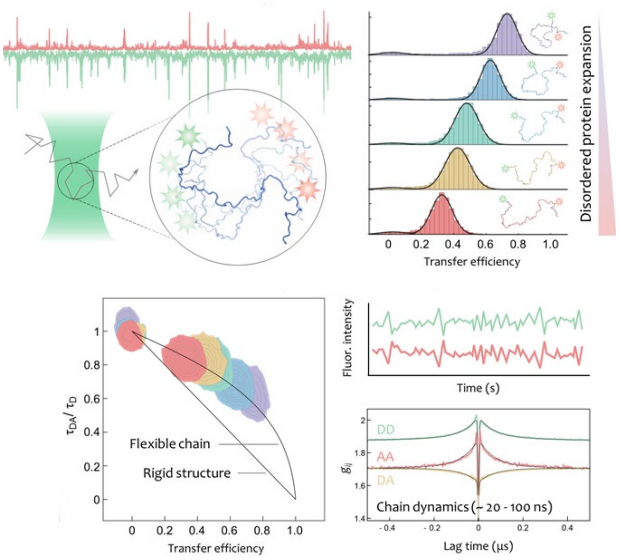


Figure 1. From detection of single biomolecules to characterization of their conformational distributions, fluctuations and dynamics

Disordered initiation factors – fine-tuners of the early steps of translation initiation

Translation initiation is directly regulated by the cap-binding complex (eIF4F), which recognizes and associates with the 5' terminal cap of mRNA and prepares it for the recruitment of the ribosome. eIF4F consists of three different proteins, so called translation initiation factors eIF4E, eIF4G and eIF4A. eIF4E is responsible for direct recognition of mRNA methyl-guanosine cap. eIF4A is an ATP-driven RNA helicase that unwinds secondary structures surrounding the 5'-end of mRNA. eIF4G serves as a scaffold for assembly of eIF4F, directly interacting with both eIF4E and eIF4A (Jackson, Hellen et al. 2010). In addition, eIF4F complex associates with eIF4B and eIF4H, which possess several crucial regulatory roles in translation initiation (Parsyan 2014). In a concerted action, these factors prepare a "landing pad" and facilitate the recruitment of the 43S pre-initiation complex and scanning the mRNA towards the start-codon recognition and ribosome assembly.

Despite the large number of binding partners (initiation factors, mRNA, rRNA) and important functionality in vivo, eIF4B (and eIF4H) are predicted to be predominantly disordered (Uversky 2014) and can be termed as disordered translation initiation factors (DisIFs). We focus on investigation of these proteins, and aim at understanding their behavior, interactions and mechanistic basis for function in translation initiation.

Disordered initiation factors and their relation to LLPS and stress granules

It is currently emerging that many aspects of intracellular organization are performed through formation of membrane-less condensates (Banani, Lee et al. 2017). The main driving force for condensate assembly is believed to be the intracellular LLPS (Shin and Brangwynne 2017). Currently many independent observations point that IDPs or proteins with long IDRs are key drivers of cellular LLPS (Dignon, Best et al. 2020).

Cellular condensates form under action of various stimuli. For example, stress granules (SGs) form during cellular stress and are responsible for subcellular storage of stress-inhibited translation machinery and stabilization of naked mRNAs (Protter and Parker 2016).

Recent evidences indicate an enrichment of translation initiation factors, among which DisIFs (eIF4B, eIF4H), within the proteome of SGs (You, Huang et al. 2020), whereas their exact roles therein are currently unknown. We primarily focus on understanding of the behavior and function of DisIFs in LLPS and assembly of SGs. On the other hand, we aim to expand the current understanding of the general laws determining IDP-driven condensate formation and underlying specificity and selectivity mechanisms.

Selected publications

1. Aznauryan, M.; Noer, S. L.; Pedersen, C. W.; Mergny, J.-L.; Teulade-Fichou, M.-P.; Birkedal, V. Ligand Binding to Dynamically Populated G-Quadruplex DNA. *Chembiochem* **2021**, 22 (10), 1811–1817. https://doi.org/10.1002/cbic.202000792.

Fondation Bettencourt Schueller
Reconnue d'utilité publique depuis 1987

Dr. Valérie Gabelica
Research Director (DR2), INSERM

Valérie Gabelica studied Chemistry and obtained her PhD in Sciences in 2002 at the University of Liège. After a postdoc in Frankfurt as Humboldt fellow, she rejoined the Mass Spectrometry Laboratory in Liège where she obtained a permanent position as FNRS research associate in October 2005. She joined the IECB in 2013 with the support of an Atip-Avenir grant, and became an Inserm research director (DR2) in December 2013. She obtained an ERC Consolidator grant in 2014. Her main research interests are fundamental aspects of mass spectrometry and its application to non-covalent complexes in general and nucleic acid complexes in particular, with research themes spanning from physical chemistry to biophysics and structural chemistry and biology.

Research team

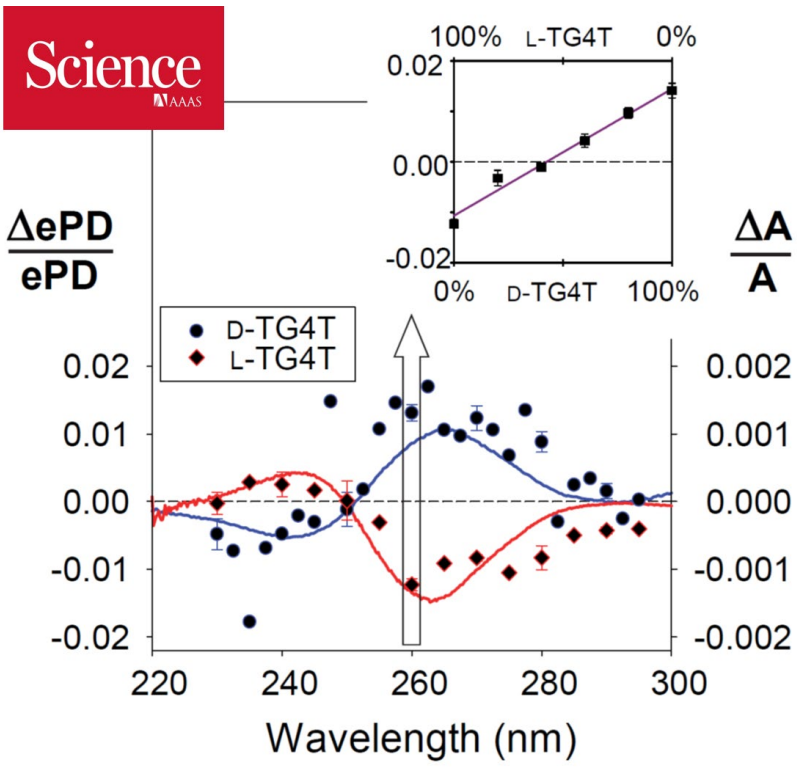
Dr. Valérie GABELICA Research Director DR2 (INSERM)
Dr. Eric LARGY Maître de Conférences (Univ. Bordeaux)
Dr. Nina KHRISTENKO Post-doc (INSERM)
Dr. Sanae BENABOU ZDAOU IdEX post-doc (Univ. Bordeaux)
Dr. Debasmita GHOSH Post-doc (INSERM)
Dr. Aram HONG Post-doc, National Research Foundation of Korea (Univ. Chungbuk)
Alexander KÖNIG PhD student (Univ. Bordeaux)
Matthieu RANZ M1 student (INSERM Bordeaux)
Jessy ERIALC M2 student (Univ. de Lille)
Prof. Derek WILSON IdEX visiting scholar, on sabbatical (Univ. York)
Mirial GUZMAN LORITE Visiting PhD student (Univ. of Alcala)

This team is part of the unit "Acides Nucléiques: Régulations Naturelles et Artificielles" (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

Mass Spectrometry of Nucleic Acids & Supramolecular Complexes

Our team focuses on the measurement sciences applied to non-covalent interactions. Nucleic acids (and more recently, foldamers and protein therapeutics) are our model systems and systems on which we learn new things. Our aim is to decipher the relationships between structures and energetics—Angstroms and Calories—in non-covalent complexes. Non-covalent interactions govern the structure and function of myriads of systems, from supramolecular assemblies to biological complexes. High-resolution structural methods help to understand what interactions are at stake in specific states of well-defined assemblies. Yet function is linked to energetics: How prevalent is a structural form? How does it switch to other states? How fast? To bridge the gap between structure and energetics, our team develops new mass spectrometry approaches to separate, quantify, and structurally characterize the different ensembles of structures (the different states) simultaneously present in solution.

In mass spectrometry, our team contributes to establish more solid ground to interpret ion mobility spectrometry experiments in terms of structure. Unexpected results have led us to challenge the paradigm claiming that non-covalent interactions are always well maintained in the gas phase. It turns out that this assertion was based on a bias favoring the publication of positive results. We highlighted the importance of structural changes related to the electrospray ionization process. The dissemination of these research results at numerous international conferences, as well as the publication of recommendations (Gabelica et al., *Mass Spectrom. Rev.* 2019), has had an impact on many developers and users of these methodologies, both academic and industrial.



Another highlight is the first ever circular dichroism spectra of biomolecules trapped in a mass spectrometer. This is a totally new way to characterize chirality using mass spectrometry. This work has been published in Science (2020). We used mass spectrometry to isolate ions of guanine-rich DNA sequences that form G-quadruplexes, then irradiate the DNA with laser pulses of given wavelength, polarization, and energy. The laser light causes electrons to detach from the DNA ions, a process that changes the ions' charge state. We switch between different polarizations of light and a CD spectrum from difference in electron photodetachment as a function of the polarization and wavelength. The shapes of gas-phase CD spectra of various DNA structures were similar to conventional solution-phase CD spectra of the same structures, which suggests that the gas- and solution-phase structures have similar base-stacking patterns. Using the new method, we could distinguish between antiparallel and hybrid conformations of the same DNA sequence. The new approach can be extended to study proteins and protein aggregates, for example to determine the α-helix/β-sheet fraction in distinct oligomer stoichiometries, but such use will require overcoming challenges such as signal-to-noise issues.

In the field of nucleic acid biophysics, our team demonstrated the feasibility of probing nucleic acid structures by in-solution hydrogen/deuterium exchange mass spectrometry (*Largy & Gabelica, Anal. Chem.* 2020). This approach has a bright future to help us obtain dynamical insight into nucleic acid complexes, through the quantitative analysis of the exchange rates. Besides, we published a comprehensive database of G-quadruplexes for native mass spectrometry in potassium *(Ghosh et al., NAR 2021)*, wherein we thoroughly document the solution topology of G-quadruplexes in MS-compatible conditions.

Selected publications

1. Porrini, M.; Rosu, F.; Rabin, C.; Darré, L.; Gómez, H.; Orozco, M.; Gabelica, V. Compaction of Duplex Nucleic Acids upon Native Electrospray Mass Spectrometry. *ACS Cent Sci* **2017**, 3 (5), 454-461. https://doi.org/10.1021/acscentsci.7b00084.

2. Ghosh, A.; Largy, E.; Gabelica, V. DNA G-Quadruplexes for Native Mass Spectrometry in Potassium: A Database of Validated Structures in Electrospray-Compatible Conditions. *Nucleic Acids Res* **2021**, 49 (4), 2333-2345. https://doi.org/10.1093/nar/gkab039.

3. Largy, E.; König, A.; Ghosh, A.; Ghosh, D.; Benabou, S.; Rosu, F.; Gabelica, V. Mass Spectrometry of Nucleic Acid Noncovalent Complexes. *Chem Rev* **2022**, 122 (8), 7720-7839. https://doi.org/10.1021/acs.chemrev.1c00386.

4. Daly, S.; Rosu, F.; Gabelica, V. Mass-Resolved Electronic Circular Dichroism Ion *Spectroscopy. Science* **2020**, 368 (6498), 1465-1468. https://doi.org/10.1126/science.abb1822.

5. Largy, E.; Gabelica, V. Native Hydrogen/Deuterium Exchange Mass Spectrometry of Structured DNA Oligonucleotides. *Anal Chem* **2020**, 92 (6), 4402-4410. https://doi.org/10.1021/acs.analchem.9b05298.

6. Gabelica, V. Native Mass Spectrometry and Nucleic Acid G-Quadruplex Biophysics: Advancing Hand in Hand. *Acc Chem Res* **2021**, 54 (19), 3691-3699. https://doi.org/10.1021/acs.accounts.1c00396.

7. Winnerdy, F. R.; Bakalar, B.; Das, P.; Heddi, B.; Marchand, A.; Rosu, F.; Gabelica, V.; Phan, A. T. Unprecedented Hour-Long Residence Time of a Cation in a Left-Handed G-Quadruplex. *Chem Sci* **2021**, 12 (20), 7151-7157. https://doi.org/10.1039/d1sc00515d.

European Research Council

Solid-state NMR of Molecular Assemblies

Dr. Antoine Loquet
Research Director (DR), CNRS

Antoine Loquet graduated from the University of Lyon / Ecole Normale Supérieure de Lyon. He did his PhD (2006-2009) under the guidance of Anja Böckmann (IBCP Lyon), working on the development of Solid-State NMR to solve protein structures. In 2008 he joined the group of Beat Meier (ETH Zürich) to study prion fibrils by Solid-State NMR. He then focused his research on molecular assemblies by Solid-State NMR as an EMBO postdoctoral fellow with Adam Lange at the Max Planck Institute for Biophysical Chemistry (Göttingen, Germany). There, he developed Solid-State NMR methods to determine atomic structures of large biological supramolecular assemblies. He obtained a CNRS position in 2013 at the CBMN (Institute of Chemistry & Biology of Membranes & Nanoobjects) in Bordeaux. In 2014, he was recruited as a group leader at the IECB and since 2016, he is leading the group "NMR of Membranes and Protein Assemblies" at CBMN. His current research concentrates on the structural investigation of molecular assemblies using Solid-State NMR. He obtained an ERC Starting Grant in 2015. He is CNRS Research Director since 2020.

Research team

Antoine LOQUET Research Director, DR (CNRS)
Axelle GRÉLARD Research Engineer, IR CNRS
Mélanie BERBON Engineer, IE (CNRS)
Dr. Yann FICHOU Researcher, CRCN (CNRS)
Dr. Corinne SANCHEZ McF U. Bordeaux (Univ. Bordeaux)
Dr. Birgit HABENSTEIN CR CNRS (CNRS)
Dr. Erick DUFOURC Emeritus Research Director, (CNRS)
Bilal MUHAMMED PhD (Univ. Bordeaux)
Loic Delcourte PhD (CNRS)
Fatjona Xhango IE (CNRS)
Coralie ROBERT PhD (CNRS)
Zeren Xu PhD (CNRS)

This team is part of the unit "CBMN UMR5248 CNRS/Univ. Bordeaux /Bordeaux INP

Self-assembly is a fundamental process by which individual subunits assemble into ordered macromolecular entities, such as filaments, fibrils, oligomers, tubes or nanomachines. In biology, protein assemblies are involved in crucial cellular processes, ranging from the propagation of neurological disorders to viral and bacterial infections. The group aims at investigating atomic structures, and assembly processes of such sophisticated assemblies. We develop and apply solid-state NMR to capture structural and dynamic details at the atomic scale. Our group is also involved in the production of large protein assemblies to solve their structures based on solid-state NMR methods. Molecular assemblies either involved in cellular processes or engineered by supramolecular chemistry constitute the current research activities.

High resolution structure of amyloid fibrils:
Neurodegenerative disorders are frequently associated with β-sheet-rich amyloid deposits. Amyloid-forming proteins can aggregate under different structural conformations known as strains, which can exhibit a prion-like behavior and distinct pathophenotypes. Precise molecular determinants defining strain specificity and cross-strain interactions (cross-seeding) are currently unknown. The HET-s prion protein from the fungus Podospora anserina represents a model system to study the fundamental properties of prion amyloids. Here, we report the amyloid prion structure of HELLF, a distant homolog of the model prion HET-s. We find that these two amyloids, sharing only 17% sequence identity, have nearly identical β-solenoid folds but lack cross-seeding ability in vivo, indicating that prion specificity can differ in extremely similar amyloid folds. We engineer the HELLF sequence to explore the limits of the sequence-to-fold conservation and to pinpoint determinants of cross-seeding and prion specificity. We find that amyloid fold conservation occurs even at an exceedingly low level of identity to HET-s (5%). Next, we derive a HELLF-based sequence, termed HEC, able to breach the cross-seeding barrier in vivo between HELLF and HET-s, unveiling determinants controlling cross-seeding at residue level. These findings show that virtually identical amyloid backbone structures might not be sufficient for cross-seeding and that critical side-chain positions could determine the seeding specificity of an amyloid fold. Our work redefines the conceptual boundaries of prion strain and sheds light on key molecular features concerning an important class of pathogenic agents.

Results published in Daskalov et al., PNAS 2021.

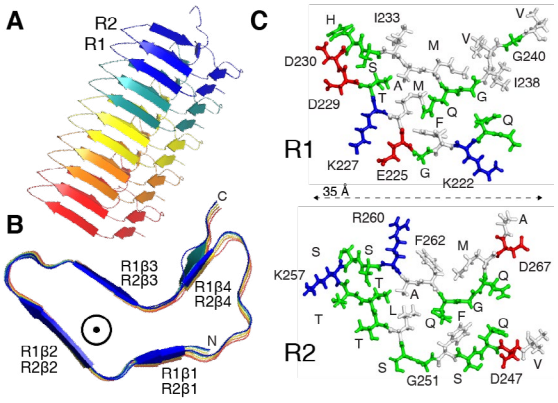


Figure: Solid-state NMR structure of HELLF amyloid fibrils

Magic-angle spinning NMR methodological development:

Solid-state NMR spectroscopy is a powerful technique to study insoluble and non-crystalline proteins and protein complexes at atomic resolution. The development of proton (1H) detection at fast magic-angle spinning (MAS) has considerably increased the analytical capabilities of the technique, enabling the acquisition of 1H-detected fingerprint experiments in few hours. Here an approach based on double-quantum (DQ) 13C spectroscopy, detected on 1H, is proposed for fast MAS regime (> 60 kHz) to perform the sequential assignment of insoluble proteins of small size, without any specific deuteration requirement. By combining two three-dimensional 1H detected experiments correlating a 13C DQ dimension respectively to its intra-residue and sequential 15 N-1H pairs, a sequential walk through DQ (Ca + CO) resonance is obtained. The approach takes advantage of fast MAS to achieve an efficient sensitivity and the addition of a DQ dimension provides spectral features useful for the resonance assignment process.

Results published in Lends et al., JBNMR 2021.

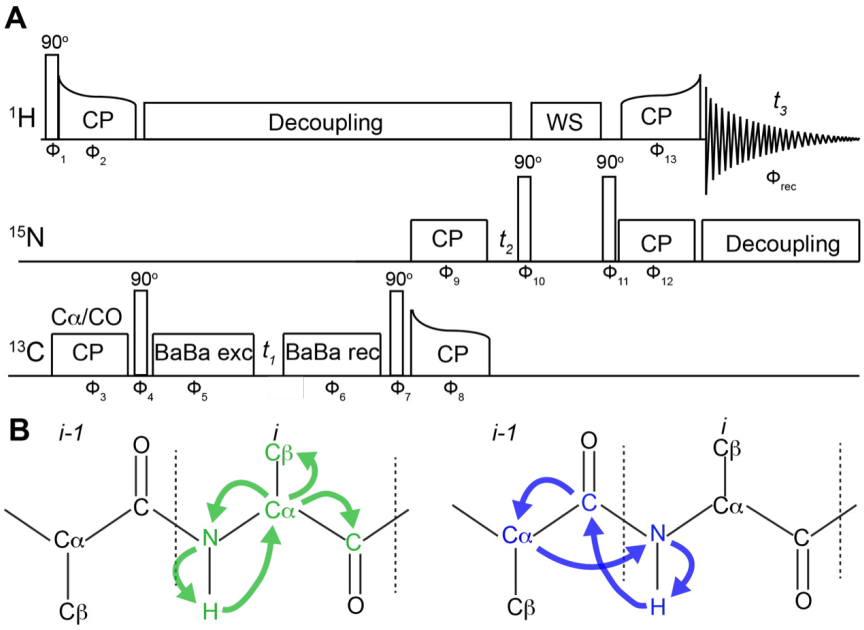


Figure: Development of a solid-state NMR approach to assign insoluble protein assemblies.

NMR applied to wine science:

We apply solution NMR and solid-state NMR to respectively investigate the impact of lipids on tannins and to characterize the effect of bacteria on wine wood. Results have been published in Saad et al., J. Agric. Food. Chem 2021 and Haidar et al., Environ. Microbiol. 2021.

Selected publications

1. Haidar, R.; Yacoub, A.; Vallance, J.; Compant, S.; Antonielli, L.; Saad, A.; Habenstein, B.; Kauffmann, B.; Grélard, A.; Loquet, A.; Attard, E.; Guyoneaud, R.; Rey, P. Bacteria Associated with Wood Tissues of Esca-diseased Grapevines: Functional Diversity and Synergy with Fomitiporia Mediterranea to Degrade Wood Components. *Environ Microbiol* **2021**, 23 (10), 6104-6121. https://doi.org/10.1111/1462-2920.15676.

2. Latxague, L.; Benizri, S.; Gaubert, A.; Tolchard, J.; Martinez, D.; Morvan, E.; Grélard, A.; Saad, A.; Habenstein, B.; Loquet, A.; Barthélémy, P. Bolaamphiphile-Based Supramolecular Gels with Drugs Eliciting Membrane Effects. *Journal of Colloid and Interface Science* **2021**, 594, 857-863. https://doi.org/10.1016/j.jcis.2021.03.026.

3. Saad, A.; Bousquet, J.; Fernandez-Castro, N.; Loquet, A.; Géan, J. New Insights into Wine Taste: Impact of Dietary Lipids on Sensory Perceptions of Grape Tannins. *J. Agric. Food Chem.* **2021**, 69 (10), 3165-3174. https://doi.org/10.1021/acs.jafc.0c06589.

4. Lends, A.; Berbon, M.; Habenstein, B.; Nishiyama, Y.; Loquet, A. Protein Resonance Assignment by Solid-State NMR Based on 1H-Detected 13C Double-Quantum Spectroscopy at Fast MAS. *J Biomol NMR* **2021**, 75 (10-12), 417-427. https://doi.org/10.1007/s10858-021-00386-6.

5. Daskalov, A.; Martinez, D.; Coustou, V.; El Mammeri, N.; Berbon, M.; Andreas, L. B.; Bardiaux, B.; Stanek, J.; Noubhani, A.; Kauffmann, B.; Wall, J. S.; Pintacuda, G.; Saupe, S. J.; Habenstein, B.; Loquet, A. Structural and Molecular Basis of Cross-Seeding Barriers in Amyloids. *Proc. Natl. Acad. Sci. U.S.A.* **2021**, 118 (1), e2014085118. https://doi.org/10.1073/pnas.2014085118.

Dr. Derek McCusker
Research Director (DR2), CNRS

Derek McCusker studied Immunology at Glasgow University and focused on the role of the proteasome in immunity in Prof. John Trowsdale's lab at Cancer Research UK for his thesis. During postdoctoral work with Dr Robert Arkowitz at the Laboratory of Molecular Biology in Cambridge he became interested in the control of cell growth. He then joined Prof. Douglas Kellogg's group at the University of California, Santa Cruz, where he investigated how cells coordinate cell growth and cell division. He was recruited by CNRS in 2009 and joined IECB as a group leader. Here, he obtained his habilitation in 2013 from the University of Bordeaux and since 2017 he has been a Director of Research with the CNRS. The group uses interdisciplinary approaches to study the dynamics of cell growth during the cell cycle.

Research team

Dr. Derek McCUSKER Research Director DR2 (CNRS)
Landry PEYRAN PhD student (Univ. Bordeaux)
Laetitia GOULEME Assistant Engineer (Univ. Bordeaux)

This team is part of the unit "Institut de Biochimie et Genetiques Cellulaire" (IBGC), CNRS UMR5095/Univ. Bordeaux"

Dynamics of Cell Growth & Division

Cells grow, duplicate their genome and divide via a series of events collectively termed the cell cycle. Coordination between the cell cycle machinery and proteins that regulate cell growth ensure the fidelity of cell division; however, the underlying mechanisms are unclear. In humans, failure of these control mechanisms has been directly linked to tumour formation. The goal of the Cell Growth and Division Laboratory is to understand how cell growth is controlled and how growth is coordinated with cell cycle progression in the model eukaryote *Saccharomyces cerevisiae.* These fundamental questions are addressed using cutting-edge interdisciplinary approaches.

1. Cellular Self-organization – generating order from the abyss.
Living matter can be distinguished from inanimate matter such as liquids and gasses by virtue of the propensity of living systems to self-organize. This entails the use of energy dissipation to drive multiple components within living cells far from thermodynamic equilibrium (e.g. polymers of tubulin or actin). By coupling polymerization/depolymerization cycles to regulatory components, living cells are endowed with remarkable and unique properties: the ability to grow, move and self-replicate. Some signaling components within cells that display characteristics of self-organization are becoming amenable to purification and reconstitution, and thus a more thorough understanding. Examples of self-organized processes within cells and the regulatory mechanisms controlling them are discussed in this review. This invited Perspective was published in MBoC in 2020.

2. Phosphatidylserine and GTPase activation control Cdc42 nanoclustering to counter dissipative diffusion.
All cells establish a single polarity axis that enables chromosomes to be equally partitioned into the mother and daughter cell at the end of each cell cycle. Defects in the establishment of a single polarity axis are directly linked to tumourogenesis. Cdc42 is an essential, conserved polarity regulator in all eukaryotes examined. In budding yeast, Cdc42 localization defines the cell's polarity axis by determining where the cell will grow and divide during the cell cycle. The mechanisms ensuring that Cdc42 concentrates at a single site to define the cell's polarity axis are incompletely understood. Here, we used high-density single protein tracking combined with photoactivation localization microscopy (sptPALM) to monitor Cdc42 dynamics and organization at single molecule resolution in budding yeast (Figure 1). We found that the mobility of Cdc42 was reduced at the pole of the cell compared with other regions of the membrane. This is important, since reduced mobility would stabilize the protein at the pole, helping to concentrate it there and establish a robust polarity axis. We found that Cdc42 is organized in very small "nanoclusters" and that these clusters are larger at the cell pole than elsewhere on the plasma membrane (Figure 1, inset). Two factors were identified that control Cdc42 mobility and promote its nanoclustering: the activation of the GTPase and a specific lipid called phosphatidylserine that is enriched at the cell pole. Phosphatidylserine appears to promote Cdc42 nanoclustering via a scaffold protein called Bem1 that interacts with Cdc42, and that we previously demonstrated boosts the activation of Cdc42. These studies reveal how the mobility of a Rho GTPase is controlled to counter the depletive effects of diffusion, thus stabilizing Cdc42 on the plasma membrane and sustaining cell polarity. This work was published in MBoC in 2018.

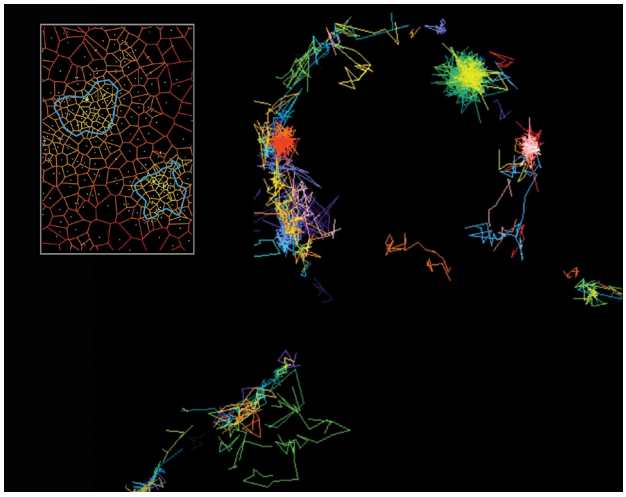


Figure 1. Single molecule imaging of Cdc42 in budding yeast. On the right, each track displays a single molecule localization. Note how some Cdc42 molecules are highly confined (geen, pink and orange) while others are free to diffuse. Inset displays single molecule localizations in white and Cdc42 nanoclusters in blue.

3. Avidity-driven polarity axis establishment via multivalent lipid-GTPase module interactions.

While Rho GTPases are indispensible regulators of cellular polarity, the mechanisms underlying their anisotropic activation at membranes have been elusive. Using the budding yeast Cdc42 GTPase module, which includes a Guanine nucleotide Exchange Factor (GEF) Cdc24 and the scaffold Bem1, we found that avidity generated via multivalent anionic lipid interactions is a critical mechanistic constituent of polarity establishment. We identifed basic cluster (BC) motifs in Bem1 that drive the interaction of the scaffold-GEF complex with anionic lipids including phosphatidylserine at the cell pole. This interaction appears to influence lipid acyl chain ordering, thus regulating membrane rigidity and feedback between Cdc42 and the local membrane environment. Sequential mutation of the Bem1 BC motifs, PX domain and the PH domain of Cdc24 led to a progressive loss of cellular polarity stemming from defective Cdc42 nanoclustering on the plasma membrane and perturbed GTPase signaling (Figure 2). Our work demonstrates the importance of avidity via multivalent anionic lipid interactions in the spatial control of GTPase activation. Dr. Julien Meca, a PhD student in the lab, was awarded the 2019 Monique Garnier-Semancik prize for the best Life Science thesis by the Univ. of Bordeaux for his contribution to this work. The study was a collaboration between the McCusker and Loquet teams at IECB. The study was also selected as being of outstanding interest to the field by a 2020 review in Current Opinion in Cell Biology (together with the Rapali et al paper published by the team in eLife in 2017).

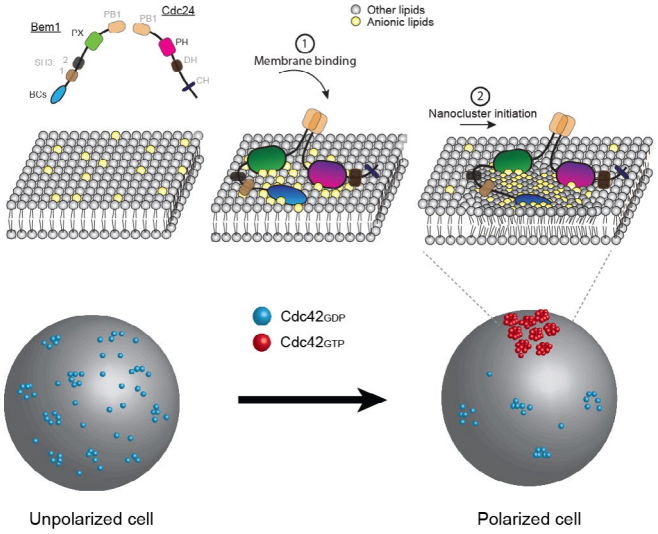


Figure 2. Schematic illustrating the relationship between Cdc42 regulators and the membrane environment during the establishment of a polarity axis. 1) The Bem1-Cdc24 complex is recruited to the plasma membrane via multivalent interactions with anionic lipids such as phosphatidylserine. The BC motifs in Bem1 provide the strongest affinity for anionic lipids at this step. 2) Upon their recruitment to anionic lipids, the Bem1 BC motifs may influence the local membrane environment, contributing to local Cdc42 activation by Cdc24 and Cdc42 nanoclustering.

Selected publications

1. Meca, J.; Massoni-Laporte, A.; Martinez, D.; Sartorel, E.; Loquet, A.; Habenstein, B.; McCusker, D. Avidity-driven Polarity Establishment via Multivalent Lipid- GTP Ase Module Interactions. *EMBO J* **2019**, 38 (3). https://doi.org/10.15252/embj.201899652.

2. McCusker, D. Cellular Self-Organization: Generating Order from the Abyss. *MBoC* **2020**, 31 (3), 143-148. https://doi.org/10.1091/mbc.E19-04-0207.

3. Sartorel, E.; Ünlü, C.; Jose, M.; Massoni-Laporte, A.; Meca, J.; Sibarita, J.-B.; McCusker, D. Phosphatidylserine and GTPase Activation Control Cdc42 Nanoclustering to Counter Dissipative Diffusion. *MBoC* **2018**, 29 (11), 1299-1310. https://doi.org/10.1091/mbc.E18-01-0051.

4. Rapali, P.; Mitteau, R.; Braun, C.; Massoni-Laporte, A.; Ünlü, C.; Bataille, L.; Arramon, F. S.; Gygi, S. P.; McCusker, D. Scaffold-Mediated Gating of Cdc42 Signalling Flux. *eLife* **2017**, 6, e25257. https://doi.org/10.7554/eLife.25257.

Dr. Anne Royou
Research Director (DR2), CNRS

Following a bachelor degree in physiology and cell biology, Anne Royou did a postgraduate degree in molecular and cellular genetics at the Université Paris XI. She did her PhD thesis under the guidance of Dr. Roger Karess, at the Centre de Génétique Moléculaire in Gif-sur-Yvette, studying the role of non-muscle myosin II during development in Drosophila. Following her PhD, she joined Dr. William Sullivan's lab at the University of California, Santa Cruz, as a post-doctoral fellow. There, she became interested in the mechanisms that preserve genome integrity during cell division. She obtained a CNRS permanent position in 2009, an ATIP/Avenir grant in 2010 and was recruited as a team leader at IECB in 2011. In 2013 she was awarded an ERC starting grant. In 2016 she was promoted DR2 by the CNRS.

Research team

Dr. Anne ROYOU Team Leader (CNRS)
Marie-Charlotte CLAVERIE Assistant Engineer (Univ. Bordeaux)
Dr. Emilie MONTEMBAULT Researcher (CNRS)
Irène Deduyer PhD (CNRS)
Noluen Touly M1 (CNRS)

This team is part of the "Institut de Biochimie et Génétique Cellulaire" (IBGC), CNRS/Université de Bordeaux (UMR5095)

Control & Dynamics of Cell Division

The mechanisms that safeguard cells against aneuploidy are of great interest as aneuploidy contributes to tumorigenesis. Using live imaging approaches, we have identified two novel mechanisms that permit the accurate transmission of chromosomes during cell division. The first mechanism involves the faithful segregation of damaged chromosomes. Our studies reveal that chromosome fragments segregate properly to opposite poles. This poleward motion is mediated through DNA tethers that connect the chromosome fragments. The second mechanism involves the coordination of chromosome segregation with cell cleavage. We found that cells can adapt to trailing chromatids by elongating transiently during anaphase. This Myosin-mediated mechanism ensures the clearance of chromatids from the cleavage plane at the appropriate time during cytokinesis, thus preserving genome integrity.

Mitosis is the final stage of the cell cycle where a copy of the duplicated genome condensed into chromosomes is transmitted to each daughter cell. Failure to do so produces daughter cells with an inappropriate genome content, also called aneuploidy. The mechanisms that safeguard cells against aneuploidy are of great interest as aneuploidy contributes to tumorigenesis. Our group has identified two novel mechanisms that permit the accurate transmission of chromosomes during cell division. The first mechanism involves the faithful segregation of damaged chromosomes. The second mechanism coordinates chromosome segregation with cell cleavage.

Mechanism that permits faithful transmission of broken chromosomes

The presence of DNA damage, such as DNA double-strand breaks (DSB), triggers the activation of the DNA Damage Response, which delays the cell cycle and promotes DNA repair. While the DNA damage response is well documented in interphase, less is known about the response to DSB during mitosis. The presence of DSB during mitosis is particularly challenging for the cell as it produces broken chromosomes lacking a centromere. This situation can cause genomic instability due to improper segregation of the broken fragments into daughter cells. Our team has uncovered a process by which broken chromosomes are faithfully transmitted, via the tethering of the two broken chromosome ends. We demonstrate that the mitotic proteins Polo, BubR1 and Bub3 accumulate on DSB during mitosis and facilitate the proper segregation of the broken chromosome fragments. This requires the BubR1-mediated sequestration Fizzy, a co-factor of the E3 ubiquitin ligase Anaphase-promoting-complexe/cyclosome (APC/C) and the subsequent local inhibition of the APC/C at the site of damage.

The DSB sensor, Mre11-Rad50-Nbs1 complex, and Polo kinase are recruited to DNA lesions during mitosis. However, their mechanism of recruitment is elusive. Using live-cell imaging combined with the micro-irradiation of single chromosomes, we analysed the dynamics of Polo and Mre11 at DNA lesions during mitosis. The two proteins display distinct kinetics. While Polo kinetics at DSBs are Cdk1-driven, Mre11 promptly but briefly associates with DSBs regardless of the phase of mitosis and re-associates with DSBs in the proceeding interphase. Mechanistically, Polo kinase activity is required for its own recruitment and that of the mitotic proteins BubR1 and Bub3 to DSBs. Moreover, depletion of Rad50 severely impaired Polo kinetics at mitotic DSBs. Conversely, ectopic tethering of Mre11 to chromatin is sufficient to recruit Polo. Our study highlights a novel pathway that links the DSB sensor MRN complex and Polo kinase to initiate a prompt, decisive response to the presence of DNA damage during mitosis.

Mechanism that coordinates chromosome segregation with cell cleavage

Chromosome segregation must be coordinated with cell division to ensure proper transmission of the genetic material into daughter cells. Our group identified a novel mechanism by which Drosophila neuronal stem cells coordinate chromosome segregation with cell division. Cells adapt to the presence of trailing chromatids at the site of division by transiently, but dramatically, elongating during anaphase, thus facilitating the clearance of the trailing chromatids from the cleavage plane. This adaptive elongation depends on myosin activity and the Rho Guanine-nucleotide exchange factor, Pebble. Cells promote the clearance of trailing chromatids from the cleavage site by undergoing two phases of adaptive elongation. The first phase relies on assembly of a wide contractile ring at the onset of cytokinesis. The second phase requires outward flux of myosin from the ring toward the polar cortex during ring constriction. Myosin efflux is a novel feature of cytokinesis and its duration is coupled to nuclear envelope reassembly (NER) and the ensuing nuclear sequestration of Pebble. Trailing chromatids induce a delay in NER concomitant with a prolonged period of cortical myosin activity, thus providing forces for the second adaptive elongation. The cytoplasmic retention of Pebble is sufficient to prolong myosin efflux and promote elongation in the absence of trailing chromatids. We propose that the modulation of cortical myosin dynamics is part of the cellular response triggered by an anaphase checkpoint that delays NER when trailing chromatids are present at the midzone.

Selected publications

1. Chinoy, Z. S.; Montembault, E.; Moremen, K. W.; Royou, A.; Friscourt, F. Impacting Bacterial Sialidase Activity by Incorporating Bioorthogonal Chemical Reporters onto Mammalian Cell-Surface Sialosides. *ACS Chem. Biol.* **2021**, 16 (11), 2307–2314. https://doi.org/10.1021/acschembio.1c00469.

2. Landmann, C.; Pierre-Elies, P.; Goutte-Gattat, D.; Montembault, E.; Claverie, M.-C.; Royou, A. The Mre11-Rad50-Nbs1 Complex Mediates the Robust Recruitment of Polo to DNA Lesions during Mitosis. *Journal of Cell Science* **2020**, jcs.244442. https://doi.org/10.1242/jcs.244442.

Dr. David Santamaria
Group leader (DR2), INSERM

David Santamaría received his PhD from University Autónoma of Madrid (Spain) in 1999, under the guidance of Prof. Jorge B. Schwartzman, studying replication fork barriers. He then joined the laboratory of Prof. Ronald A. Laskey, (1999-2003) at the Wellcome/CRC Institute (Cambridge, UK) where he dealt with the initiation of DNA replication and its connection with cell cycle control. He returned to Spain (2003-2016) as a staff scientist in Prof. Mariano Barbacid group (CNIO, Madrid) where he used mouse genetics to conduct a comprehensive analysis of the Cyclin Dependent Kinase family and to identify therapeutic targets in lung adenocarcinoma. He joined the IECB in 2016 and obtained a DR2 INSERM position starting January 2018. Since December 2021 he joined the Cancer Research Center (CIC) faculty in Salamanca, Spain.

Research team

Dr. David SANTAMARIA Research Director DR2 Inserm U1218/ (Univ. Bordeaux)
Dr. Marie-Julie NOKIN Postdoc (Univ. Bordeaux)
Dr. Tra-Ly NGUYEN Postdoc (Univ. Bordeaux)
Elodie DARBO Ingénieur de Recherche en Bioinformatique Inserm U1218/(Univ. Bordeaux)
Sonia SAN JOSÉ Assistante Ingénieur (Univ. Bordeaux)
Sergio DE HITA PhD student (Univ. Bordeaux)

This team is part of the unit Actions for onCogenesis understanding and Target Identification in Oncology) "ACTION", Inserm U1218/Univ. Bordeaux

Novel Mediators in Lung Oncogenesis

We use mouse models and engineered cellular systems to characterize new signalling pathways and oncogenic functions that govern the onset of lung adenocarcinoma (LUAD). We have a particular interest in the mechanisms that regulate the initiation, intensity and duration of the RAS-ERK signalling output. The activity of this pathway is an essential feature controlling tumour initiation, disease progression and drug resistance to several targeted agents. Our work has identified a key role of KRAS membrane dimerization/clusterization in this process. Our immediate goal is to understand the molecular basis underlying this feature and to functionally characterize yet unknown protein factors required to assemble a KRAS-dependent signalling platform on the inner plasma membrane. As a whole, this approach may identify novel therapeutic targets with low toxicity and potential clinical applicability in LUAD.

KRAS is the most frequent oncogenic driver in human cancer. Remarkably, in May 2021 the first direct inhibitors received approval by the FDA and EMA and are currently used in the clinic for the treatment of a specific KRAS mutation (G12C). Innovative therapeutic approaches are urgently needed to suppress cancer driven by other KRAS oncogenic variants. In this context, mounting evidences indicate that KRAS dynamics at the inner cell membrane and the formation of KRAS dependent membrane clusters are important regulatory steps controlling its activity both in health and disease. These observations potentially identify the building blocks of these structures as novel therapeutic targets for the treatment of KRAS driven cancers.

We are currently conducting a multidisciplinary approach aimed at identifying and characterizing potential structural co-factors required for the formation and/or stabilization of KRAS-dependent signalling clusters at the inner cell membrane. In collaboration with experts at the Bordeaux Imaging Center (BIC) we are using FLIM/FRET and single-molecule localization microscopy approaches (SPT) to follow the dynamics and membrane trajectories of KRAS-containing complexes. Also, in collaboration with colleagues at the IECB Fred Friscourt and Emmanuelle Thinon we are using protein-specific localized crosslinking (based on amber suppression) to identify new membrane interactors of KRAS using cross-linking/mass spectrometry. In a similar fashion, we collaborated with Stephanie Cabantous (CRCT, Toulouse) in the generation a flexible fluorescent cellular system compatible with high-throughput approaches that will be key to monitor and quantify KRAS dimerization/oligomerization in cells. This will be key to validate by gain & loss of function experiments the candidates identified in our crosslinking and genetic (see below) approaches. Furthermore, we are currently using this cellular system to perform a high-throughput screening of compounds in search of molecules that prevent KRAS dimerization.

Similarly, we have used a genetic approach to demonstrate a quantitative relationship between the activity of RAS-ERK (MAPK pathway) signalling with cancer transformation and progression. It is also a key factor implicated in resistance to targeted therapies and disease relapse. We have developed a genetic cellular system that provides the right selective pressure to carry out an unbiased Crispr/Cas9 screen in search of novel regulators of the RAS-MAPK signaling pathway. This approach will contribute to elucidating new control mechanisms with cancer relevance. Indeed, the screen has identified novel mechanisms of MAPK signalling output that could mediate the onset of resistance to agents targeting this pathway in the clinic. These novel mechanisms are currently being validated combining established cell lines, patient derived xenografts from tumour biopsies and sequencing data from drug resistant cancers.

Finally, conventional chemotherapy remains an important clinical weapon to treat lung cancer. We are studying factors that might modulate the response to such cytotoxic regimens and additional treatments that could be implemented to improve therapeutic success **(Figure 1)**.

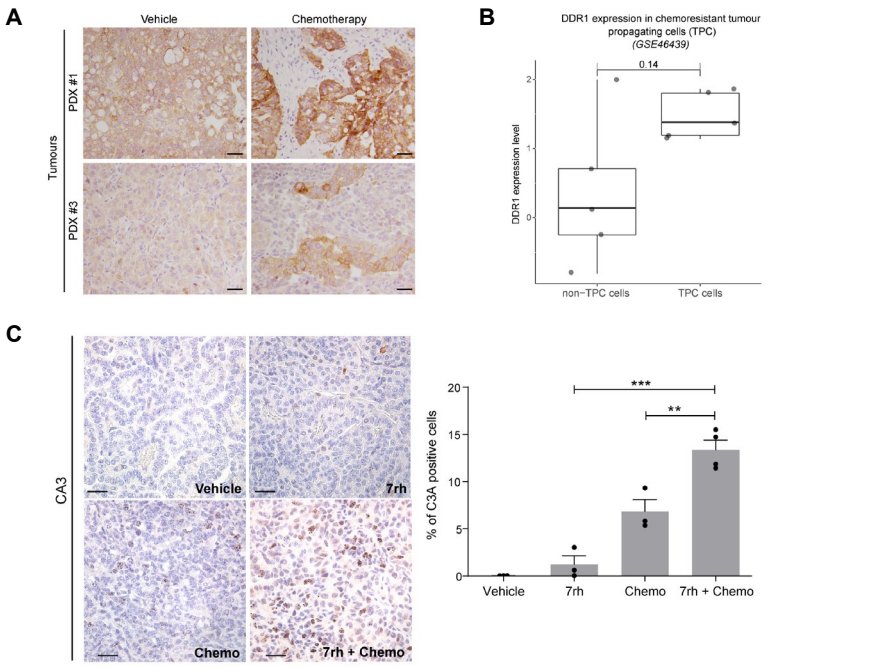


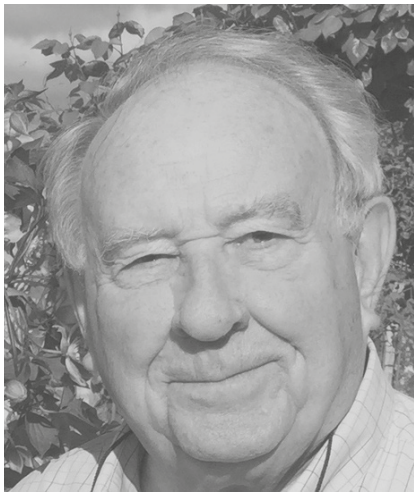
Figure 1: ***A)*** *Crl:NU-Foxn1nu mice implanted with KRAS-mutant patient derived xenografts (PDX) were treated with either vehicle or standard chemotherapy based on cisplatin (3 mg/kg) and paclitaxel (20 mg/kg) administered i.p. every 5 days for 3 weeks (n=6). After necropsy, tumour samples were fixed and analyzed for DDR1 expression by immunostaining. Clones showing high DDR1 expression are observed in the chemotherapy-treated tumours. Scale bar: 50 µm.* ***B)*** *Differential DDR1 expression in chemoresistant tumour propagating cells (TPCs) vs. the tumour bulk population (non-TPC). Gene expression data was obtained from GSE46439. Wilcoxon's test P value is indicated above the box plots.* ***C)*** *Left: representative immunostaining of the apoptotic marker active caspase-3 (C3A) in sections obtained from mice harbouring KRasG12V endogenous lung tumours (n=6 mice per group) following the indicated treatments (note 7rh is a DDR1 kinase inhibitor). Scale bar: 50 µm. Right: quantification of C3A+ cells. Data were analyzed using 1-way ANOVA followed by Bonferroni's multiple comparison test and shown as the mean ± SEM. **P < 0.01, ***P < 0.001.*

Selected publications

1. Ricciuti, B.; Son, J.; Okoro, J. J.; Mira, A.; Patrucco, E.; Eum, Y.; Wang, X.; Paranal, R.; Wang, H.; Lin, M.; Haikala, H. M.; Li, J.; Xu, Y.; Alessi, J. V.; Chhoeu, C.; Redig, A. J.; Köhler, J.; Dholakia, K. H.; Chen, Y.; Richard, E.; Nokin, M.-J.; Santamaria, D.; Gokhale, P. C.; Awad, M. M.; Jänne, P. A.; Ambrogio, C. Comparative Analysis and Isoform-Specific Therapeutic Vulnerabilities of KRAS Mutations in Non-Small Cell Lung Cancer. *Clinical Cancer Research* **2022**, 28 (8), 1640–1650. https://doi.org/10.1158/1078-0432.CCR-21-2719.

2. Nokin, M.-J.; Darbo, E.; Travert, C.; Drogat, B.; Lacouture, A.; San José, S.; Cabrera, N.; Turcq, B.; Prouzet-Mauleon, V.; Falcone, M.; Villanueva, A.; Wang, H.; Herfs, M.; Mosteiro, M.; Jänne, P. A.; Pujol, J.-L.; Maraver, A.; Barbacid, M.; Nadal, E.; Santamaría, D.; Ambrogio, C. Inhibition of DDR1 Enhances in Vivo Chemosensitivity in KRAS-Mutant Lung Adenocarcinoma. *JCI Insight* **2020**, 5 (15), e137869. https://doi.org/10.1172/jci.insight.137869.

3. Sanclemente, M.; Nieto, P.; Garcia-Alonso, S.; Fernández-García, F.; Esteban-Burgos, L.; Guerra, C.; Drosten, M.; Caleiras, E.; Martinez-Torrecuadrada, J.; Santamaría, D.; Musteanu, M.; Barbacid, M. RAF1 Kinase Activity Is Dispensable for KRAS/P53 Mutant Lung Tumor Progression. *Cancer Cell* **2021**, 39 (3), 294–296. https://doi.org/10.1016/j.ccell.2021.01.008.



Pr. Léon Ghosez

Professor Emeritus UCL, Visiting Scientist IECB, Univ. Bordeaux

Léon Ghosez was born in Aalst, Belgium, in 1934. He studied at the University of Louvain where he got a PhD in 1958 under the supervision of Prof. G. Smets,. He then spent 2 years as postdoctoral researcher at Harvard University (Prof. R.B. Woodward) and also collaborated for a few months with Prof. R. Huisgen in the Department of chemistry of the University of Münich He got his "Habilitation" at the age of 32 for his independent work on the stereochemistry of synthesis and rearrangement of halocyclopropanes. In 1969 he became "Professeur Ordinaire" at the University of Louvain where he created the laboratory of organic synthesis. During his career in Louvain (1963-1999) he supervised the research of 125 PhD students and 135 postdoctoral associates. He also hold appointments at the University of Liége (1969-1999) and the Ecole Polytechnique in Palaiseau (1993-1999). He took an active part in the creation of IECB where he established a research group in 1998. Since 2000, he shared the directorship of IECB with Dr J.J. Toulmé. Since 2011 he is an invited scientist in the same Institute. His current research interests include the design and total synthesis of biologically active molecules and the search of mild, efficient and "green" Lewis acid catalysts. In 2007, he received the medal of the Société Française de Chimie as a recognition of his support to the development of organic chemistry in France. Léon Ghosez is an emeritus member of the Royal Academy of Sciences of Belgium and a fellow of the Royal Society of Chemistry. In 2017 he received the title of "Chevalier de la Légion d'Honneur".

Research team

Dr. Léon GHOSEZ Prof. Emeritus, Invited scientist (CNRS-Univ. Bordeaux)

The team is part of the CNRS/University of Bordeaux UMR 5144 CBMN.

Organic & Medicinal Chemistry

1. Sustainable electrophilic catalysts for the activation of highly functionalized and sensitive molecules

The project aims at finding solutions to the often encountered problems associated with the use of many electrophilic catalysts: chemoselectivity, low turnover, too high molecular weight, in particular for asymmetric catalysis, toxicity and generation of much waste. New ionic solvents and silicon-derived Lewis superacids have been found to provide solutions to these problems. New electrophilic catalysts for cycloaddition and alkylation reactioins involving highly functionalized acid-sensitive molecules have been developed.

2. Deoxysubstitution of hydroxyl-containing compounds under mild and sustainable conditions : a possible practical and sustainable substitute for the Mitsonobu reaction.

The project aims at finding milder conditions for the replacement of a hydroxyl group by a nucleophile. present methods often required acidic conditions or the use of toxic reagents or(and) lead much waste (eg Mitsonobu reaction) The concept is based on earlier findings of the group on the deoxychlorination-, bromination- and iodination reactions with the readily available haloenamines : conditions are mild, atom economy is high and no reagent is toxic. The reaction was recently extended to the often pharmacologically interesting replacement of an hydroxyl group by fluorine. The plan is to extend the method to a wide variety of nucleophilic reagents including carbon nucleophiles.

Selected publications

1. Gati, W.; Munyemana, F.; Colens, A.; Srour, A.; Dufour, M.; Vardhan Reddy, K. H.; Téchy, B.; Rosse, G.; Schweiger, E.; Qiao, Q.; Ghosez, L. A Mild Method for the Replacement of a Hydroxyl Group by Halogen: 2. Unified Procedure and Stereochemical Studies. *Tetrahedron* **2020**, 76 (37), 131441. https://doi.org/10.1016/j.tet.2020.131441.

2. Munyemana, F.; Patiny, L.; Ghosez, L. A Mild Method for the Replacement of a Hydroxyl Group by Halogen: 3. the Dichotomous Behavior of α-Haloenamines towards Allylic and Propargylic Alcohols. *Tetrahedron* **2021**, 89, 132148. https://doi.org/10.1016/j.tet.2021.132148.

3. Zhu, L.; Maskeri, M. A.; Ramirez, M.; Le Bideau, F.; Ghosez, L.; Houk, K. N. Computational Exploration of Anomalous Regioselectivities in Cycloadditions of Ketenes to Oxazolines. *J. Org. Chem.* **2022**, 87 (5), 3613–3622. https://doi.org/10.1021/acs.joc.2c00001.

4. Ramirez, M.; Li, W.; Lam, Y.; Ghosez, L.; Houk, K. N. Mechanisms and Conformational Control of (4 + 2) and (2 + 2) Cycloadditions of Dienes to Keteniminium Cations. *J. Org. Chem.* **2020**, 85 (4), 2597–2606. https://doi.org/10.1021/acs.joc.9b03340.

5. Badarau, E.; Reddy, K. H. V.; Loudet, A.; Simon, C.; Trembleau, L.; Claerhout, S.; Pair, E.; Massip, S.; Breton, P.; Lesur, B.; Goldstein, S.; Fourquez, J.; Henlin, J. M.; Ghosez, L. Productive Syntheses of Privileged Scaffolds Inspired by the Recognition of a Diels–Alder Pattern Common to Three Classes of Natural Products. *Chem. Eur. J.* **2020**, 26 (67), 15477–15481. https://doi.org/10.1002/chem.202002372.

Original Peer-Reviewed Articles

1. Zaky, M. S.; Wirotius, A.-L.; Coulembier, O.; Guichard, G.; Taton, D. A Chiral Thiourea and a Phosphazene for Fast and Stereoselective Organocatalytic Ring-Opening-Polymerization of Racemic Lactide. *Chem. Commun.* **2021**, 57 (31), 3777-3780. https://doi.org/10.1039/D0CC08022E.

2. Munyemana, F.; Patiny, L.; Ghosez, L. A Mild Method for the Replacement of a Hydroxyl Group by Halogen: 3. the Dichotomous Behavior of α-Haloenamines towards Allylic and Propargylic Alcohols. *Tetrahedron* **2021**, 89, 132148. https://doi.org/10.1016/j.tet.2021.132148.

3. Meunier, T.; Desmarets, L.; Bordage, S.; Bamba, M.; Hervouet, K.; Rouillé, Y.; François, N.; Decossas, M.; Sencio, V.; Trottein, F.; Tra Bi, F. H.; Lambert, O.; Dubuisson, J.; Belouzard, S.; Sahpaz, S.; Séron, K. A Photoactivable Natural Product with Broad Antiviral Activity against Enveloped Viruses Including Highly Pathogenic Coronaviruses. *Antimicrob Agents Chemother* **2021**, AAC.01581-21. https://doi.org/10.1128/AAC.01581-21.

4. Li, G.; Ko, C.-N.; Li, D.; Yang, C.; Wang, W.; Yang, G.-J.; Di Primo, C.; Wong, V. K. W.; Xiang, Y.; Lin, L.; Ma, D.-L.; Leung, C.-H. A Small Molecule HIF-1α Stabilizer That Accelerates Diabetic Wound Healing. *Nat Commun* **2021**, 12 (1), 3363. https://doi.org/10.1038/s41467-021-23448-7.

5. Urushibara, K.; Ferrand, Y.; Liu, Z.; Katagiri, K.; Kawahata, M.; Morvan, E.; D'Elia, R.; Pophristic, V.; Tanatani, A.; Huc, I. Accessing Improbable Foldamer Shapes with Strained Macrocycles. *Chem. Eur. J.* **2021**, 27 (43), 11205-11215. https://doi.org/10.1002/chem.202101201.

6. Abidi, W.; Zouhir, S.; Caleechurn, M.; Roche, S.; Krasteva, P. V. Architecture and Regulation of an Enterobacterial Cellulose Secretion System. *Sci Adv* **2021**, 7 (5), eabd8049. https://doi.org/10.1126/sciadv.abd8049.

7. Haidar, R.; Yacoub, A.; Vallance, J.; Compant, S.; Antonielli, L.; Saad, A.; Habenstein, B.; Kauffmann, B.; Grélard, A.; Loquet, A.; Attard, E.; Guyoneaud, R.; Rey, P. Bacteria Associated with Wood Tissues of Esca-diseased Grapevines: Functional Diversity and Synergy with Fomitiporia Mediterranea to Degrade Wood Components. *Environ Microbiol* **2021**, 23 (10), 6104-6121. https://doi.org/10.1111/1462-2920.15676.

8. Mamode Cassim, A.; Navon, Y.; Gao, Y.; Decossas, M.; Fouillen, L.; Grélard, A.; Nagano, M.; Lambert, O.; Bahammou, D.; Van Delft, P.; Maneta-Peyret, L.; Simon-Plas, F.; Heux, L.; Jean, B.; Fragneto, G.; Mortimer, J. C.; Deleu, M.; Lins, L.; Mongrand, S. Biophysical Analysis of the Plant-Specific GIPC Sphingolipids Reveals Multiple Modes of Membrane Regulation. *Journal of Biological Chemistry* **2021**, 296, 100602. https://doi.org/10.1016/j.jbc.2021.100602.

9. Latxague, L.; Benizri, S.; Gaubert, A.; Tolchard, J.; Martinez, D.; Morvan, E.; Grélard, A.; Saad, A.; Habenstein, B.; Loquet, A.; Barthélémy, P. Bolaamphiphile-Based Supramolecular Gels with Drugs Eliciting Membrane Effects. *Journal of Colloid and Interface Science* **2021**, 594, 857-863. https://doi.org/10.1016/j.jcis.2021.03.026.

10. Zhu, C.; Poater, A.; Duhayon, C.; Kauffmann, B.; Saquet, A.; Rives, A.; Maraval, V.; Chauvin, R. Carbo -mer of Barrelene: A Rigid 3D-Carbon-Expanded Molecular Barrel. *Chem. Eur. J.* **2021**, 27 (36), 9286-9291. https://doi.org/10.1002/chem.202100670.

11. Liu, P.; Battie, Y.; Decossas, M.; Tan, S.; Pouget, E.; Okazaki, Y.; Sagawa, T.; Oda, R. Chirality Induction to CdSe Nanocrystals Self-Organized on Silica Nanohelices: Tuning Chiroptical Properties. *ACS Nano* **2021**, 15 (10), 16411-16421. https://doi.org/10.1021/acsnano.1c05819.

12. Collie, G. W.; Lombardo, C. M.; Yoo, S. H.; Pułka-Ziach, K.; Gabelica, V.; Mackereth, C. D.; Rosu, F.; Guichard, G. Crystal Structures Capture Multiple Stoichiometric States of an Aqueous Self-Assembling Oligourea Foldamer. *Chem. Commun.* **2021**, 57 (75), 9514-9517. https://doi.org/10.1039/D1CC03604A.

13. Bornerie, M.; Brion, A.; Guichard, G.; Kichler, A.; Douat, C. Delivery of SiRNA by Tailored Cell-Penetrating Urea-Based Foldamers. *Chem. Commun.* **2021**, 57 (12), 1458-1461. https://doi.org/10.1039/D0CC06285E.

14. Guillon, J.; Denevault-Sabourin, C.; Chevret, E.; Brachet-Botineau, M.; Milano, V.; Guédin-Beaurepaire, A.; Moreau, S.; Ronga, L.; Savrimoutou, S.; Rubio, S.; Ferrer, J.; Lamarche, J.; Mergny, J.; Viaud-Massuard, M.; Ranz, M.; Largy, E.; Gabelica, V.; Rosu, F.; Gouilleux, F.; Desplat, V. Design, Synthesis, and Antiproliferative Effect of 2,9-bis[4-(Pyridinylalkylaminomethyl)Phenyl]-1,10-phenanthroline Derivatives on Human Leukemic Cells by Targeting G-quadruplex. *Arch Pharm* **2021**, 354 (8), 2000450. https://doi.org/10.1002/ardp.202000450.

15. Ghosh, A.; Largy, E.; Gabelica, V. DNA G-Quadruplexes for Native Mass Spectrometry in Potassium: A Database of Validated Structures in Electrospray-Compatible Conditions. *Nucleic Acids Res* **2021**, 49 (4), 2333-2345. https://doi.org/10.1093/nar/gkab039.

16. Krell, K.; Pfeuffer, B.; Rönicke, F.; Chinoy, Z. S.; Favre, C.; Friscourt, F.; Wagenknecht, H. Fast and Efficient Postsynthetic DNA Labeling in Cells by Means of Strain-Promoted Sydnone-Alkyne Cycloadditions. *Chem. Eur. J.* **2021**, 27 (65), 16093-16097. https://doi.org/10.1002/chem.202103026.

17. Sweeney, T. R.; Dhote, V.; Guca, E.; Hellen, C. U. T.; Hashem, Y.; Pestova, T. V. Functional Role and Ribosomal Position of the Unique N-Terminal Region of DHX29, a Factor Required for Initiation on Structured Mammalian MRNAs. *Nucleic Acids Research* **2021**, 49 (22), 12955-12969. https://doi.org/10.1093/nar/gkab1192.

18. Kerff, F.; Liu, C.; Mu, X.; Gilbert, U.; Smal, L.; Meinertzhagen, L.; Kauffmann, B.; Robeyns, K.; Singleton, M. L. Functionalized 1,8-Diazaiptycenes as Monomers for Aromatic Oligoamide Foldamers. *ChemPlusChem* **2021**, 86 (8), 1162-1166. https://doi.org/10.1002/cplu.202100170.

19. Waltz, F.; Salinas-Giegé, T.; Englmeier, R.; Meichel, H.; Soufari, H.; Kuhn, L.; Pfeffer, S.; Förster, F.; Engel, B. D.; Giegé, P.; Drouard, L.; Hashem, Y. How to Build a Ribosome from RNA Fragments in Chlamydomonas Mitochondria. *Nat Commun* **2021**, 12 (1), 7176. https://doi.org/10.1038/s41467-021-27200-z.

20. Chinoy, Z. S.; Montembault, E.; Moremen, K. W.; Royou, A.; Friscourt, F. Impacting Bacterial Sialidase Activity by Incorporating Bioorthogonal Chemical Reporters onto Mammalian Cell-Surface Sialosides. *ACS Chem. Biol.* **2021**, 16 (11), 2307-2314. https://doi.org/10.1021/acschembio.1c00469.

21. Gauthier, M.; Koehler, V.; Clavel, C.; Kauffmann, B.; Huc, I.; Ferrand, Y.; Coutrot, F. Interplay between a Foldamer Helix and a Macrocycle in a Foldarotaxane Architecture. Angew. *Chem. Int. Ed.* **2021**, 60 (15), 8380-8384. https://doi.org/10.1002/anie.202100349.

22. Broster Reix, C. E.; Ramanantsalama, M. R.; Di Primo, C.; Minder, L.; Bonhivers, M.; Dacheux, D.; Robinson, D. R. Intrabody-Induced Cell Death by Targeting the T. Brucei Cytoskeletal Protein Tb BILBO1. *Microbiol Spectr* **2021**, 9 (2), e00915-21. https://doi.org/10.1128/Spectrum.00915-21.

23. Khemtemourian, L.; Antoniciello, F.; Sahoo, B. R.; Decossas, M.; Lecomte, S.; Ramamoorthy, A. Investigation of the Effects of Two Major Secretory Granules Components, Insulin and Zinc, on Human-IAPP Amyloid Aggregation and Membrane Damage. *Chemistry and Physics of Lipids* **2021**, 237, 105083. https://doi.org/10.1016/j.chemphyslip.2021.105083.

24. Monsarrat, C.; Compain, G.; André, C.; Engilberge, S.; Martiel, I.; Oliéric, V.; Wolff, P.; Brillet, K.; Landolfo, M.; Silva da Veiga, C.; Wagner, J.; Guichard, G.; Burnouf, D. Y. Iterative Structure-Based Optimization of Short Peptides Targeting the Bacterial Sliding Clamp. *J. Med. Chem.* **2021**, 64 (23), 17063-17078. https://doi.org/10.1021/acs.jmedchem.1c00918.

25. Atcher, J.; Mateus, P.; Kauffmann, B.; Rosu, F.; Maurizot, V.; Huc, I. Large-Amplitude Conformational Changes in Self-Assembled Multi-Stranded Aromatic Sheets. Angew. *Chem. Int. Ed.* **2021**, 60 (5), 2574-2577. https://doi.org/10.1002/anie.202014670.

26. Aznauryan, M.; Noer, S. L.; Pedersen, C. W.; Mergny, J.-L.; Teulade-Fichou, M.-P.; Birkedal, V. Ligand Binding to Dynamically Populated G-Quadruplex DNA. *Chembiochem* **2021**, 22 (10), 1811-1817. https://doi.org/10.1002/cbic.202000792.

27. Pramanik, S.; Kauffmann, B.; Hecht, S.; Ferrand, Y.; Huc, I. Light-Mediated Chiroptical Switching of an Achiral Foldamer Host in Presence of a Carbohydrate Guest. *Chem. Commun.* **2021**, 57 (1), 93-96. https://doi.org/10.1039/D0CC06484J.

28. Barba-Barba, R. M.; Chammam, M.; Ramos-Ortiz, G.; Listunov, D.; Velusamy, J.; Rodriguez, M.; Carriles, R.; Silva, C.; Duhayon, C.; Kauffmann, B.; Maraval, V.; Chauvin, R. Linear and Nonlinear Optical Properties of a Quadrupolar Carbo-Benzene and Its Benzenic Parent: The Carbo-Merization Effect. *Dyes and Pigments* **2021**, 188, 109133. https://doi.org/10.1016/j.dyepig.2021.109133.

29. Toledo, E.; Le Saux, G.; Edri, A.; Li, L.; Rosenberg, M.; Keidar, Y.; Bhingardive, V.; Radinsky, O.; Hadad, U.; Di Primo, C.; Buffeteau, T.; Smith, A.-S.; Porgador, A.; Schvartzman, M. Molecular-Scale Spatio-Chemical Control of the Activating-Inhibitory Signal Integration in NK Cells. *Sci Adv* **2021**, 7 (24), eabc1640. https://doi.org/10.1126/sciadv.abc1640.

30. Jurėnas, D.; Rosa, L. T.; Rey, M.; Chamot-Rooke, J.; Fronzes, R.; Cascales, E. Mounting, Structure and Autocleavage of a Type VI Secretion-Associated Rhs Polymorphic Toxin. *Nat Commun* **2021**, 12 (1), 6998. https://doi.org/10.1038/s41467-021-27388-0.

31. Saad, A.; Bousquet, J.; Fernandez-Castro, N.; Loquet, A.; Géan, J. New Insights into Wine Taste: Impact of Dietary Lipids on Sensory Perceptions of Grape Tannins. J. Agric. *Food Chem.* **2021**, 69 (10), 3165-3174. https://doi.org/10.1021/acs.jafc.0c06589.

32. Qi, X.; Guionneau, P.; Lafon, E.; Perot, S.; Kauffmann, B.; Mathonière, C. New Photomagnetic Ionic Salts Based on [MoIV(CN)8]4− and [WIV(CN)8]4− Anions. *Magnetochemistry* 2021, 7 (7), 97. https://doi.org/10.3390/magnetochemistry7070097.

33. Mbianda, J.; Bakail, M.; André, C.; Moal, G.; Perrin, M. E.; Pinna, G.; Guerois, R.; Becher, F.; Legrand, P.; Traoré, S.; Douat, C.; Guichard, G.; Ochsenbein, F. Optimal Anchoring of a Foldamer Inhibitor of ASF1 Histone Chaperone through Backbone Plasticity. *Sci. Adv.* **2021**, 7 (12), eabd9153. https://doi.org/10.1126/sciadv.abd9153.

34. Schäfer, P.; Gartzia-Rivero, L.; Kao, M.-T.; Schäfer, C.; Massip, S.; de Vet, C.; Raffy, G.; Del Guerzo, A. Oriented Attachment and Activated Dipoles Leading to Anisotropic H-Bond-Free Self-Assembly of n -Acene Derivatives into Organic Nanoribbons Emitting Linearly Polarised Blue Light. *J. Mater. Chem. C* **2021**, 9 (1), 136-147. https://doi.org/10.1039/D0TC04789A.

35. Bardin, T.; Daskalov, A.; Barrouilhet, S.; Granger-Farbos, A.; Salin, B.; Blancard, C.; Kauffmann, B.; Saupe, S. J.; Coustou, V. Partial Prion Cross-Seeding between Fungal and Mammalian Amyloid Signaling Motifs. *mBio* **2021**, 12 (1), e02782-20. https://doi.org/10.1128/mBio.02782-20.

36. Parrot, C.; Moulinier, L.; Bernard, F.; Hashem, Y.; Dupuy, D.; Sissler, M. Peculiarities of Aminoacyl-TRNA Synthetases from Trypanosomatids. *Journal of Biological Chemistry* **2021**, 297 (2), 100913. https://doi.org/10.1016/j.jbc.2021.100913.

37. Lends, A.; Berbon, M.; Habenstein, B.; Nishiyama, Y.; Loquet, A. Protein Resonance Assignment by Solid-State NMR Based on 1H-Detected 13C Double-Quantum Spectroscopy at Fast MAS. *J Biomol NMR* **2021**, 75 (10-12), 417-427. https://doi.org/10.1007/s10858-021-00386-6.

38. Waltz, F.; Giegé, P.; Hashem, Y. Purification and Cryo-Electron Microscopy Analysis of Plant Mitochondrial Ribosomes. *BIO-PROTOCOL* **2021**, 11 (15). https://doi.org/10.21769/BioProtoc.4111.

39. Reznichenko, O.; Cucchiarini, A.; Gabelica, V.; Granzhan, A. Quadruplex DNA-Guided Ligand Selection from Dynamic Combinatorial Libraries of Acylhydrazones. *Org Biomol Chem* **2021**, 19 (2), 379-386. https://doi.org/10.1039/d0ob01908a.

40. Delannoy López, D. M.; Tran, D. T.; Viault, G.; Dairi, S.; Peixoto, P. A.; Capello, Y.; Minder, L.; Pouységu, L.; Génot, E.; Di Primo, C.; Deffieux, D.; Quideau, S. Real-Time Analysis of Polyphenol-Protein Interactions by Surface Plasmon Resonance Using Surface-Bound Polyphenols. *Chemistry* **2021**, 27 (17), 5498-5508. https://doi.org/10.1002/chem.202005187.

41. Mateus, P.; Jacquet, A.; Méndez-Ardoy, A.; Boulloy, A.; Kauffmann, B.; Pecastaings, G.; Buffeteau, T.; Ferrand, Y.; Bassani, D. M.; Huc, I. Sensing a Binding Event through Charge Transport Variations Using an Aromatic Oligoamide Capsule. *Chem. Sci.* **2021**, 12 (10), 3743-3750. https://doi.org/10.1039/D0SC06060G.

42. Gao, J.; Okazaki, Y.; Pouget, E.; Nlate, S.; Kauffmann, B.; Artzner, F.; Buffeteau, T.; Oda, R. Slow Kinetic Evolution of Nanohelices Based on Gemini Surfactant Self-Assemblies with Various Enantiomeric Excess; Chiral Segregation towards a Racemic Mixture. *Mater. Chem. Front.* **2021**, 5 (7), 3021-3028. https://doi.org/10.1039/D0QM00989J.

43. Soufari, H.; Parrot, C.; Kuhn, L.; Waltz, F.; Hashem, Y. Specific Features and Assembly of the Plant Mitochondrial Complex I Revealed by Cryo-EM. *Nat Commun* **2020**, 11 (1), 5195. https://doi.org/10.1038/s41467-020-18814-w.

44. Belinite, M.; Khusainov, I.; Soufari, H.; Marzi, S.; Romby, P.; Yusupov, M.; Hashem, Y. Stabilization of Ribosomal RNA of the Small Subunit by Spermidine in Staphylococcus Aureus. Front. *Mol. Biosci.* **2021**, 8, 738752. https://doi.org/10.3389/fmolb.2021.738752.

45. Sobiech, T. A.; Zhong, Y.; Sánchez B., L. S.; Kauffmann, B.; McGrath, J. K.; Scalzo, C.; Miller, D. P.; Huc, I.; Zurek, E.; Ferrand, Y.; Gong, B. Stable Pseudo[3]Rotaxanes with Strong Positive Binding Cooperativity Based on Shape-Persistent Aromatic Oligoamide Macrocycles. *Chem. Commun.* **2021**, 57 (88), 11645-11648. https://doi.org/10.1039/D1CC05193H.

46. Beckert, B.; Leroy, E. C.; Sothiselvam, S.; Bock, L. V.; Svetlov, M. S.; Graf, M.; Arenz, S.; Abdelshahid, M.; Seip, B.; Grubmüller, H.; Mankin, A. S.; Innis, C. A.; Vázquez-Laslop, N.; Wilson, D. N. Structural and Mechanistic Basis for Translation Inhibition by Macrolide and Ketolide Antibiotics. *Nat Commun* **2021**, 12 (1), 4466. https://doi.org/10.1038/s41467-021-24674-9.

47. Daskalov, A.; Martinez, D.; Coustou, V.; El Mammeri, N.; Berbon, M.; Andreas, L. B.; Bardiaux, B.; Stanek, J.; Noubhani, A.; Kauffmann, B.; Wall, J. S.; Pintacuda, G.; Saupe, S. J.; Habenstein, B.; Loquet, A. Structural and Molecular Basis of Cross-Seeding Barriers in Amyloids. *Proc. Natl. Acad. Sci. U.S.A.* **2021**, 118 (1), e2014085118. https://doi.org/10.1073/pnas.2014085118.

48. van der Stel, A.-X.; Gordon, E. R.; Sengupta, A.; Martínez, A. K.; Klepacki, D.; Perry, T. N.; Herrero del Valle, A.; Vázquez-Laslop, N.; Sachs, M. S.; Cruz-Vera, L. R.; Innis, C. A. Structural Basis for the Tryptophan Sensitivity of TnaC-Mediated Ribosome Stalling. *Nat Commun* **2021**, 12 (1), 5340. https://doi.org/10.1038/s41467-021-25663-8.

49. Cussol, L.; Mauran-Ambrosino, L.; Buratto, J.; Belorusova, A. Y.; Neuville, M.; Osz, J.; Fribourg, S.; Fremaux, J.; Dolain, C.; Goudreau, S.; Rochel, N.; Guichard, G. Structural Basis for A-Helix Mimicry and Inhibition of Protein-Protein Interactions with Oligourea Foldamers. *Angew. Chem. Int. Ed.* **2021**, 60 (5), 2296-2303. https://doi.org/10.1002/anie.202008992.

50. Nottelet, P.; Bataille, L.; Gourgues, G.; Anger, R.; Lartigue, C.; Sirand-Pugnet, P.; Marza, E.; Fronzes, R.; Arfi, Y. The Mycoplasma Surface Proteins MIB and MIP Promote the Dissociation of the Antibody-Antigen Interaction. *Sci Adv* **2021**, 7 (10), eabf2403. https://doi.org/10.1126/sciadv.abf2403.

51. Winnerdy, F. R.; Bakalar, B.; Das, P.; Heddi, B.; Marchand, A.; Rosu, F.; Gabelica, V.; Phan, A. T. Unprecedented Hour-Long Residence Time of a Cation in a Left-Handed G-Quadruplex. *Chem Sci* **2021**, 12 (20), 7151-7157. https://doi.org/10.1039/d1sc00515d.

Invited Peer-Reviewed Articles

1. Nguyen, P. H.; Ramamoorthy, A.; Sahoo, B. R.; Zheng, J.; Faller, P.; Straub, J. E.; Dominguez, L.; Shea, J.-E.; Dokholyan, N. V.; De Simone, A.; Ma, B.; Nussinov, R.; Najafi, S.; Ngo, S. T.; Loquet, A.; Chiricotto, M.; Ganguly, P.; McCarty, J.; Li, M. S.; Hall, C.; Wang, Y.; Miller, Y.; Melchionna, S.; Habenstein, B.; Timr, S.; Chen, J.; Hnath, B.; Strodel, B.; Kayed, R.; Lesné, S.; Wei, G.; Sterpone, F.; Doig, A. J.; Derreumaux, P. Amyloid Oligomers: A Joint Experimental/Computational Perspective on Alzheimer's Disease, Parkinson's Disease, Type II Diabetes, and Amyotrophic Lateral Sclerosis. **Chem. Rev. 2021**, 121 (4), 2545–2647. https://doi.org/10.1021/acs.chemrev.0c01122.

2. Chinoy, Z. S.; Friscourt, F. Bioorthogonal Chemical Ligations Towards Neoglycoproteins. In **Comprehensive Glycoscience**; Elsevier, 2021; pp 660–675. https://doi.org/10.1016/B978-0-12-819475-1.00080-8.

3. Gabelica, V. CHAPTER 1. Ion Mobility–Mass Spectrometry: An Overview. In **New Developments in Mass Spectrometry**; Ashcroft, A. E., Sobott, F., Eds.; Royal Society of Chemistry: Cambridge, 2021; pp 1–25. https://doi.org/10.1039/9781839162886-00001.

4. Friscourt, F., In Science of Synthesis: Click Chemistry, Rutjes, F. P. J. T., Ed.; **Thieme: Stuttgart, (2021)**; p 641–659. https://doi.org/10.1055/sos-SD-235-00329

5. Manteca, A.; Gadea, A.; Van Assche, D.; Cossard, P.; Gillard-Bocquet, M.; Beneyton, T.; Innis, C. A.; Baret, J.-C. Directed Evolution in Drops: Molecular Aspects and Applications. **ACS Synth. Biol. 2021**, 10 (11), 2772–2783. https://doi.org/10.1021/acssynbio.1c00313.

6. Hijazo-Pechero, S.; Alay, A.; Marín, R.; Vilariño, N.; Muñoz-Pinedo, C.; Villanueva, A.; Santamaría, D.; Nadal, E.; Solé, X. Gene Expression Profiling as a Potential Tool for Precision Oncology in Non-Small Cell Lung Cancer. **Cancers 2021**, 13 (19), 4734. https://doi.org/10.3390/cancers13194734.

7. Tabbò, F.; Pisano, C.; Mazieres, J.; Mezquita, L.; Nadal, E.; Planchard, D.; Pradines, A.; Santamaria, D.; Swalduz, A.; Ambrogio, C.; Novello, S.; Ortiz-Cuaran, S. How Far We Have Come Targeting BRAF-Mutant Non-Small Cell Lung Cancer (NSCLC). **Cancer Treatment Reviews 2022**, 103, 102335. https://doi.org/10.1016/j.ctrv.2021.102335.

8. Vicens, Q.; Bochler, A.; Jobe, A.; Frank, J.; Hashem, Y. Interaction Networks of Ribosomal Expansion Segments in Kinetoplastids. In **Macromolecular Protein Complexes III**: Structure and Function; Harris, J. R., Marles-Wright, J., Eds.; Subcellular Biochemistry; Springer International Publishing: Cham, 2021; Vol. 96, pp 433–450. https://doi.org/10.1007/978-3-030-58971-4_13.

9. Largy, E.; König, A.; Ghosh, A.; Ghosh, D.; Benabou, S.; Rosu, F.; Gabelica, V. Mass Spectrometry of Nucleic Acid Noncovalent Complexes. **Chem Rev 2022**, 122 (8), 7720–7839. https://doi.org/10.1021/acs.chemrev.1c00386.

10. Sissler, M.; Hashem, Y. Mitoribosome Assembly Comes into View. **Nat Struct Mol Biol 2021**, 28 (8), 631–633. https://doi.org/10.1038/s41594-021-00640-3.

11. Gabelica, V. Native Mass Spectrometry and Nucleic Acid G-Quadruplex Biophysics: Advancing Hand in Hand. **Acc Chem Res 2021**, 54 (19), 3691–3699. https://doi.org/10.1021/acs.accounts.1c00396.

12. Waltz, F.; Corre, N.; Hashem, Y.; Giegé, P. Specificities of the Plant Mitochondrial Translation Apparatus. **Mitochondrion 2020**, 53, 30–37. https://doi.org/10.1016/j.mito.2020.04.008.

13. Daskalov, A.; El Mammeri, N.; Lends, A.; Shenoy, J.; Lamon, G.; Fichou, Y.; Saad, A.; Martinez, D.; Morvan, E.; Berbon, M.; Grélard, A.; Kauffmann, B.; Ferber, M.; Bardiaux, B.; Habenstein, B.; Saupe, S. J.; Loquet, A. Structures of Pathological and Functional Amyloids and Prions, a Solid-State NMR Perspective. Front. **Mol. Neurosci. 2021**, 14, 670513. https://doi.org/10.3389/fnmol.2021.670513.

14. Yoo, S. H.; Li, B.; Dolain, C.; Pasco, M.; Guichard, G. Urea Based Foldamers. In **Methods in Enzymology**; Elsevier, 2021; Vol. 656, pp 59–92. https://doi.org/10.1016/bs.mie.2021.04.019.

15. Abidi, W.; Torres-Sánchez, L.; Siroy, A.; Krasteva, P. V. Weaving of Bacterial Cellulose by the Bcs Secretion Systems. FEMS **Microbiol Rev 2022**, 46 (2), fuab051. https://doi.org/10.1093/femsre/fuab051.

Prizes, Awards

- European Biophysical Societies' Association (EBSA) Prize and Medal, EBSA, Y. Hashem
- DCO Prize, Société Chimique de France, 2021, G. Guichard
- Prix Liliane Bettencourt pour les Sciences du Vivant, Fondation Bettencourt Schueller, 2021, V. Gabelica
- Heinrich Emanuel Merck Award for Analytical Science, Merck KGaA, Darmstadt, Germany, 2022, V. Gabelica
- Ampere Prize, Ampere society, 2021, A. Loquet
- Best poster prize, Canceropole South West Annual conference, 2021, L. Peyran

Evaluation Boards

- Membre de section, Comité National de la Recherche scientifique – Section 16, 021, G. Guichard
- Panel member, ERC AdG 2020 – PE04, 2020–2021, V. Gabelica
- Commission scientifique spécialisée (titulaire nommé), CSS1 – Inserm, 2022–2026, V. Gabelica
- Rapporteur, Thesis committee, 2021, A. Royou
- Examinateur, Thesis committee, 2021, A. Royou
- Examinateur, Mid-thesis committee, 2021, A. Royou
- Examinateur, Mid-thesis committee, 2021, A. Royou
- Member of Axe1, grant evaluator, GSO canceropole, 2021, D. Santamaria

Journal & Scientific Society Boards

- Peptide Science (Wiley), 2021, G. Guichard
- President, Aquitaine section of the Société de Chimie de France (SCF), 2021, G. Guichard
- Scientific Council, Société de Chimie Thérapeutique (SCT), 2021, G. Guichard
- Team member, SCT Young MedChem Forum – YMCF, 2021, G. Guichard
- Associate Editor, Analytical Chemistry (ACS), 2021–2023, V. Gabelica
- Board member, Molecules, 2021, A. Loquet
- Ediitor & reviewer, Frontiers in Cell & Developmental Biology, 2021, D. McCusker

Teaching

- Microbiology 2H, Cours de microbiologie génrale insititut Pasteur, 2020, R. Fronzes
- Organic chemistry, Methods and scientific communication, Professional orientation – Total of 96h, BSc Level (L1 STS chimie, L3 STS chimie), 2021, F. Friscourt
- Chimie générale, Chimie organique, Biomolécules du vivant, Biologie Chimique : 192 HETD, BSc Level (L1 SVSTC Chimie, L2 SVSTC Chimie), MSc Level (M1 MMF/COSV Chimie du vivant, M2 COSV biologie chimique, 2020, C. Dolain
- Chimie générale, chimie organique, vectorisation, peptides bioactifs, sondes en imagerie, chimie thérapeutique : 192 HETD, PACES (Première Année Commune aux Etudes de Santé), cursus pharmacie 2ème année et 3ème année, module chimie du double cursus "Ecole Santé Sciences" (2ème année de pharmacie, odontologie et médecine), Master 2 TECSAN. Coresponsabilité du module de chimie du double cursus "Ecole Santé Sciences", 2020, G. Compain
- 2nd year ENSTBB – 8h30, Characterization of biomolecules by SPR, 2021, C. Di Primo
- Master 1 Biochimie Univ. Bordeaux – 4h, Analysis of the interactions by SPR, 2021, C. Di Primo
- L3 TecSan Univ. Bordeaux – 14h, Instrumentations: SPTR technology, 2021, C. Di Primo
- Docteur en pharmacie: Sciences analytique – 96 h, Acid/base, oxidoreduction, potentiometry, buffers, precipitation, coordination, UV-vis spectroscopy, IR spectroscopy, GC, HPLC, liquid-liquid extraction, E. Largy
- Docteur en pharmacie: Apprentissage des techniques et gestes de base – 18 h, Basic lab technics, E. Largy
- DEUST Production, contrôles et qualité des produits de santé : Chimie analytique – 25.5 h, Acid/base, oxidoreduction, potentiometry, buffers, precipitation, coordination, E. Largy
- DEUST Production, contrôles et qualité des produits de santé : Réglementaire – 10.5 h, Regulatory aspects of drug quality control in the pharma industry, E. Largy
- Master 2 Analyse Chimique et Contrôle Qualité des Médicaments et Autres Produits de Santé & Master 2 Analytical chemistry for Drugs and Natural Products : Qualification – 3 h, Qualification of analytical instruments in regulated environment, E. Largy
- Master 2 Analyse Chimique et Contrôle Qualité des Médicaments et Autres Produits de Santé & Master 2 Analytical chemistry for Drugs and Natural Products : Recherche et développement analytique – 9 h, HPLC/UPLV analytical method development and transfer in pharma R&D. Detectors (MS, UV, fluorescence, Corona, LS,…), pumps, advanced column applications, E. Largy
- Master 2 Analyse Chimique et Contrôle Qualité des Médicaments et Autres Produits de Santé & Master 2 Analytical chemistry for Drugs and Natural Products : Contrôle qualité appliqué au produit fini – 15 h, Characterization and quantitation of drug substance and impurities by HPLC, E. Largy
- Master 2 Analyse Chimique et Contrôle Qualité des Médicaments et Autres Produits de Santé : Projet tuteuré en laboratoire ou contrat en entreprise – 35 h, Mentoring of students in the pharmaceutical industry,
- Master 2 Analyse Chimique et Contrôle Qualité des Médicaments et Autres Produits de Santé : Validation – 5 h, Analytical method validation, E. Largy
- Master 2 Analyse Chimique et Contrôle Qualité des Médicaments et Autres Produits de Santé : Management et gestion de projet – 12 h, Project management, E. Largy
- MAPI – 4 h, Supporting the emergence and restructuring of new projects – Health sciences, E. Largy
- Projet SAN STEP – 14 h, Pedagogical innovations: Teaching online, on modern media (online quizzes, video presentations, analytical toolbox website,…), E. Largy
- Jury VAE – 1 h, Jury for the validation of knowledge acquisition through professional experience (pharmaceutical analysis), E. Largy
- IDEX/ANA: Projet IDEX Analytical Chemistry for drugs and natural product – 7.5, Pedagogical innovations: teaching in English, E. Largy
- Préparateurs en pharmacie hospitalière – 3 h, Solution chemistry, E. Largy
- NMR spectroscopy, 6h, 2021, A. Loquet
- Drosophila as a model organism, Master 1 program, 2021, A. Royou
- Master 2 Université de Bordeaux, Génétique Moléculaire et Cellulaire (GMC), 2021, D. Santamaria
- Master 2 Université de Bordeaux, UER Cytogénétique et Biologie Moléculaire des tumeurs, 2021, D. Santamaria

PhD Theses

- Elodie LEROY, "Mechanisms of Context-Dependent Translation Inhibition by Ribosome-Targeting Antibiotics", European Union (ERC), A. INNIS, University of Bordeaux, 2021

- Wiem ABIDI, Structural and Functional "Studies of Bacterial Cellulose Secretion" ED ITFA, ERC H2020 BioMatrix, to P.V. Krasteva, Université Paris-Saclay, 2021

Science & Society

- Fêtes de la Science, Bordeaux, France, octobre 2020, R. Fronzes

- Half-day outreach activity at Lycée Le Grand, Bordeaux, organized through the association "Declics", Bordeaux, France, November/2021, E. Thinon, C. Freyermuth

Team Funding

European and International fundings

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher(s)	Funding body	Research project	Period
R. Fronzes	ERC	Structure and Function of the Bacterial Transformasome	2017-2022
Y. Hashem	ERC	Translation regulation in eukaryotic pathogens and hosts	2018-2023
A. Innis	ERC	Ribosome inhibition by nascent or antimicrobial peptides	2017-2022
A. Innis	JPI-AMR	Development of novel ribosome-targeting antibiotics	2019-2022
P.V. Krasteva	ERC	Structural Biology of Exopolysaccharide Secretion in Bacterial Biofilms	2018-2023
N. Reyes	ERC	Transport and Receptor Mechanisms of Human Solute Carriers	2018-2023
N. Reyes	NIH	The mechanism of allosteric modulation of glutamate transporters	2019-2024
G. Guichard	EU	Metal-Foldamer Porous Frameworks	2021-2023
C. Di Primo	Euskampus	Fundamental insights into binding mechanisms for the rational design of sensors for the detection of SARS-CoV-2	2021-2022
C. Di Primo	EuroNanomed	Monitoring of Acquired Brain Injury and recovery biomarkers by the combined label-free nanoSensing of multiple circulating molecules	2019-2022
D. Santamaria	Fundacio La Marato	Modulating glycemia to improve benefit of chemoradiotherapy and immunotherapy in Non- Small Cell Lung Carcinoma	2020-2022

National funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Research project	Period
R. Fronzes	ANR	Dissecting the Antibody Cleavage System of Mycoplasmas	2018-2021
R. Fronzes	ANR	Structural basis of Helicobacter pylori type IV secretion system	2019-2022
R. Fronzes	ANR	Une approche multidisciplinaire pour comprendre la structure et la dynamique du système de sécrétion de type VI	2020-2024
R. Fronzes	EquipEX+	Microscopie corrélative à haute résolution en conditions cryogéniques	2021-2027
Y. Hashem	ANR	Translation initiation in plant mitochondria	2021-2025
Y. Hashem	ANR	ABC-F mediated antibiotic resistance	2020-2024
Y. Hashem	ANR	Mitochondrial translation in plants	2018-2022
P.V. Krasteva	ANR	Role Of C-di-GMP in the Kinetics of legionella Effector Translocation – ROCKET	2022-2025
F. Friscourt	CNRS ATIP-Avenir	Making the invisible, visible, detecting traumatic brain injury	2017-2021
G. Guichard	ANR	Mode d'action dual: Nouveaux antimicrobiens ciblant la réplication et la traduction	2022-2025
G. Guichard	ANR	Therapeutic targeting and chemical biology of histone chaperone using rationally designed medium-size inhibitors	2021-2025
G. Compain	ANR JCJC	Selective and directional supramolecular interactions based on highly polar fluorinated synthons	2021-2025
E. Thinon	ANR	Chemical approaches to study the S-palmitoylation of a host factor in Influenza A virus infection	2021-2024
M. Aznauryan	ANR JCJC	Probing the molecular mechanisms of function of disordered translation initiation factors: from in vitro to in-cell	2021-2025
V. Gabelica	ANR	Understanding Native Electrospray of Artificial and Natural Polymers	2019-2022
A. Loquet	ANR	Transkingamyloid	
A. Loquet	MITI CNRS	Molecular dynamics of amyloid cross-seeding	2020-2022
D. McCusker	Ministry of research	Cell polarity & nuclear dynamics	2020-2023
A. Royou	ANR	Spatial regulation of RhoGTPase during cell division	2022-2026
D. Santamaria	INCA-Plbio	Targeting KRAS dimerization in advanced lung adenocarcinoma	2019-2022
E. Largy	ANR JCJC	Hydrogen / denterium exchange mass spectrome try of nucleic acids	2021-2025

Regional funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Type of funding	Period
Y. Hashem	IdEx Bordeaux	IdEx Junior Chair: Translation régulation in pathogens and hosts	2017-2021
P.V. Krasteva	U-Bordeaux	Structure and regulation of exopolysaccharide secretion	2019-2023
N. Reyes	Idex Bordeaux	Membrane protein mechanisms	2019-2024
N. Reyes	Region Nouvelle Aquitaine	Membrane protein mechanisms	2020-2025
F. Friscourt	LabEx TRAIL	Traumatic Brain Injury Glycobiomarker	2019-2021
F. Friscourt	Canceropole GSO	Chemo-enzymatic elaboration of well-defined oligosaccharides as galectin inhibitors for cancer therapy	2019-2021
F. Friscourt / M. Aznauryan	IECB	Probing the conformation, dynamics and protein recognition of single glycans	2021
G. Guichard	Region Nouvelle Aquitaine	Nouveaux outils pour l'optimisation et le développement de peptides thérapeutiques : Application au ciblage thérapeutique des chaperons d'histones	2021-2023
G. Compain	Region Nouvelle Aquitaine	Interactions supramoléculaires sélectives et directionnelles basées sur des synthons fluorés hautement polaires	2021-2023
E. Thinon	University of Bordeaux	Chemical approaches to decipher the role of a host factor in Influenza A virus internalization	2019-2023
E. Thinon	Region Nouvelle Aquitaine	Caractérisation d'une nouvelle cible thérapeutique antivirale	2020-2025
E. Thinon / A. Innis	IECB & STS Department University of Bordeaux	A toolbox to tag and characterize small proteins in bacteria.	2021
M. Aznauryan	Region Nouvelle Aquitaine	Caractérisation des mécanismes moléculaires gouvernant la fonction d'eIF4B : vers de nouvelles cibles contre le cancer	2020-2023
S. Benabou	IdEx Bordeaux	Exploring the biophysical properties of DNA i-motif structures by native mass spectrometry and ion mobility spectrometry	2019-2021
V. Gabelica	Region Nouvelle Aquitaine	Caractériser le repliement de protéines thérapeutiques recombinantes par spectrométrie de mobilité ionique	2019-2024
D. J. Wilson	IdEx Bordeaux	Conformational Dynamics and Promiscuous Ligand Selection in Human La Protein/RNA Interactions	2020-2021
A. König / V. Gabelica	MESRI	PhD fellowship	2020-2023
P. Sarkis / M. Aznauryan	ED SVS/MESRI	PhD fellowship	2021-2024

Charity-funded research projects

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Charity	Research project	Period
V. Gabelica	Fondation Bettencourt Schueller	New mass spectrometry approaches to reveal how covalent modifications modulate the stability of regulatory DNA or RNA	2021-2024
A. Royou	FRM	Spatiotemporal control of a novel RhoGEF isoform during cell cleavage	2021-2024

Contracts with the industry

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Company	Research contract	Period
G. Guichard	Ureka Pharma		2021-2023
V. Gabelica	Merck Biodevelopment SAS	Caractériser le repliement de protéines thérapeutiques recombinantes par spectrométrie de mobilité ionique	2019-2022

Collaborations

Pole 1 – Structural biology

Structure and Function of Bacterial Nanomachines
Dr. Rémi Fronzes

- Dr. Nicolas Reyes, UMR5234 MFP, Bordeaux, France
- Dr. Yonathan Arfi, INRAE, Biologie du Fruit et Pathologie, UMR 1332, Villenave D'ornon, France
- Dr. Eric Cascales, LISM CNRS UMR7255, Marseille, France
- Dr. Laure Journet, LISM CNRS UMR7255, Marseille, France
- Dr. Laurent Terradot, IBCP, Lyon, France

RNA Processing and translation regulation in pathogens and hosts
Dr. Yaser Hashem

- Dr. Philippe Giegé, CNRS, Strasbourg, France
- Dr. Hakim Mireau, INRA, Versaille, France
- Dr. Tatyana Pestova, SUNY Downstate Medical Center, Brooklyn, NY, USA
- Dr. Christopher Helen, SUNY Downstate Medical Center, Brooklyn, NY, USA
- Dr. Laurence Drouard, CNRS, Strasbourg, France
- Dr. Marat Yusupov, Inserm, Strasbourg, France
- Dr. Pascale Romby, CNRS, Strasbourg, France

Translational Regulation of Gene Expression
Dr. Axel Innis

- Prof. Nora VÁZQUEZ-LASLOP, University of Illinois at Chicago, Chicago, USA
- Prof. Alexander MANKIN, University of Illinois at Chicago, Chicago, USA
- Prof. Luis Rogelio CRUZ-VERA, University of Alabama in Huntsville, Huntsville, USA
- Prof. Matthew SACHS, Texas A&M University, College Station, USA
- Prof. Daniel WILSON, University of Hamburg, Hamburg, Germany
- Prof. Helmut GRUBMÜLLER, MPI for Multidisciplinary Sciences, Göttingen, Germany
- Prof. Jean-Christophe BARET, CNRS – CRPP, Bordeaux, France

Structural Biology of Biofilms
Dr. Petya Krasteva

- Dr. Yoshiharu Yamaichi, I2BC, Gif-sur-Yvette, France
- Dr. Jean-Marc Ghigo, Institut Pasteur, Paris, France

Membrane Protein Mechanisms
Dr. Nicolas Reyes

- Prof. Julia Chamot-Roo, Institut pasteur/CNRS, Paris, France
- Prof. Jan Steyaert, VIB/VUB Brussel, Brussels, Belgium
- Scientist Pierre Legrand, SOLEIL Synchrotron, Paris, France

Pole 2 – Organic & bioorganic chemistry

Chemical Neuroglycobiology
Dr. Frédéric Fiscourt

- Prof. Kelley Moremen, University of Georgia, CCRC, Athens, GA, USA
- Dr. Anne Royou, IBGC, CNRS UMR5095, Univ. Bordeaux, Bordeaux, France
- Prof. Hans-Achim Wagenknecht, Karlsruhe Institute of Technology, Karlsruhe, Germany

Peptidomimetic Chemistry
Dr. Gilles Guichard

- Dr. Françoise Ochsenbein, Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS, Université Paris-Saclay, Gif-sur-Yvette, France
- Dr. Natacha Rochel, Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), INSERM, U1258/CNRS, UMR 7104/, Univ. Strasbourg, Illkirch, France
- Dr. Gavin Collie, Discovery Sciences, R&D, AstraZeneca, Cambridge, UK
- Dr. Dominique Burnouf, Université de Strasbourg, CNRS, Architecture et Réactivité de l'ARN, UPR 9002, Institut de Biologie Moléculaire et Cellulaire du CNRS, 2 rue Conrad Roentgen, F-67000 Strasbourg, France, Strasbourg, France
- Dr. Jérôme Wagner, Biotechnologie et Signalisation Cellulaire, UMR 7242 CNRS/Université de Strasbourg, ESBS, Illkirch, France
- Dr. Céline Douat, Department of Pharmacy and Center for Integrated Protein Science, Ludwig-Maximilians-Universität, München, Germany
- Dr. Antoine Kichler, CAMB 7199 CNRS, Equipe 3Bio, Faculté de Pharmacie, Université de Strasbourg, Illkirch, France
- Prof. Daniel Taton, Laboratoire de Chimie des Polymères Organiques (LCPO), Université de Bordeaux, INP-ENSCBP, Pessac, France
- Dr. Valérie Gabelica, Univ. Bordeaux, CNRS, INSERM, ARNA, UMR 5320, U1212, IECB, Pessac, France
- Dr. Frédéric Rosu, Univ. Bordeaux, CNRS, INSERM, IECB, UMS 3033, Pessac, France
- Dr. Cameron Mackereth, Univ. Bordeaux, CNRS, INSERM, ARNA, UMR 5320, U1212, IECB, Pessac, France
- Dr. Sébastien Goudreau, Ureka Pharma SAS, Pessac, France

Pole 3 - Biophysics

Single-molecule Biophysics
Dr. Mikayel Aznauryan

- Prof. Sébastien Lecommandoux, LCPO, University of Bordeaux, Pessac, France
- Prof. Stéphane Quideau, CNRS, University of Bordeaux, Talence, France
- Dr. Derrick Robinson, CNRS, University of Bordeaux, Bordeaux, France
- Dr. Guillaume Le Saux, Ben-Gurion University, Beer-Sheva, Israel
- Prof. Dik-Lung Ma, Hong Kong Baptist University, Hong Kong, China

Mass Spectrometryof Nucleic Acids & Supramolecular Complexes
Dr. Valérie Gabelica

- Dr. Marie-Paule Teulade-Fichou, Institut Curie, CNRS UMR176, Centre Universitaire Paris XI, Orsay, France
- Dr. Anton Granzhan, Institut Curie, CNRS UMR176, Centre Universitaire Paris XI, Orsay, France
- Dr. Yann Ferrand, UMR 5248 CBMN, Pessac, France
- Prof. Anh Tuan Phan, Nanyang Technical University, Singapore, Singapore
- Prof. Janez Plavec, National Institute of Chemistry, Ljublkana, Slovenia

Solid-state NMR of Molecular Assemblies
Dr. Antoine Loquet

- Dr. NISHIYAMA Yusuke, JEOL, Yokohama, Japan
- Prof. REY Patrice, Université Pau, IPREM, Pau, France
- Prof. BARTHELEMY Philippe, ARNA, Bordeaux, France
- Dr. SAUPE Sven, IBGC, Bordeaux, France
- Dr. PINTACUDA Guido, CRMN, Lyon, France
- Dr. WALL Joseph, Brookhaven, Upton, USA
- Dr. BARDIAUX Benjamin, Institut Pasteur, Paris, France

Pole 4 - Molecular & cellular biology

Control & dynamics of cell division
Dr. Anne Royou

- Dr. Friscourt Frédéric, University of Bordeaux, Bordeaux, France

Novel mediators in lung oncogenesis
Dr. David Santamaria

- Dr. Ernest Nadal, Idibell, Barcelona, Spain
- Dr. Chiara Ambrogio, Molecular Biotechnology Center (MBC) University of Torino, Torino, Italy
- Prof. Mariano Barbacid, Spanish National Cancer Centre (CNIO), Madrid, Spain

Invited Conferences

Pole 1 – Structural biology

RNA Processing and translation regulation in pathogens and hosts

- ZOMES XI CONFERENCE, Magdeburg, Germany, 2022, August 31-September 3, Y. Hashem
- The Ribosome Conference 2022, Bordeaux, France, 2022, Jully 10-14, Y. Hashem
- Groupe Français de Bioénérgetique, Virtual, France, 2021, September 21-24, Y. Hashem
- 13th European Biophysics Conference EBSA, Vienna, Austria, 2021, August 24-28, Y. Hashem
- Translational Control Meeting CSH, Cold Spring Harbor, NY, USA, 2022, September 5-10, Y. Hashem
- Joachim Frank Honorary Symposium, Columbia Unversity, NYC, NYC, USA, 2022, September 5-5, Y. Hashem

Translational Regulation of Gene Expression

- EMBO YIP Annual Meeting, Online, 06/2021, A. Innis
- EYSF 2021 – EMBO Young Scientists Forum, Warsaw, Poland, 10/2021, A. Innis
- BSI 2021 – 2nd French Congress on Integrative Structural Biology, Paris-Saclay Campus, France, 11/2021, A. Innis

Structural Biology of Biofilms Group

- ASM Microbe and FEMS World Microbe Forum – Poster Presentation, Virtual / Global, 2021, P. V. Krasteva
- French Microbiology Day – Speaker, Virtual Minisymposium / France, 2021, P. V. Krasteva

Membrane Protein Mechanisms

- Transmembrane Transporter Society International Meeting, Copenhagen, Copenhagen, Denmark, June/2022, N. Reyes
- Gordon Research Conference "Ligand Recognition and Gating", Toscana/Italy, March/2022, N. Reyes
- CryoEM symposium EMBL, Heidelberg/Germany, February/2020, N. Reyes

Pole 2 – Organic & bioorganic chemistry

Peptidomimetic Chemistry

- Journée de Printemps de la Division de Chimie Organique (DCO) de la Société Chimique de France, Paris, 04/2022, G. Guichard
- Indian Peptide Symposium, Bangalore (Virtual), 03/2021, G. Guichard
- WISC Workshop in Supramolecular Chemistry, Cagliari, 09/2021, C. Dolain

Chemical Biology of membrane proteins

- First interdisciplinary meeting in cancer research, Oncosphere Nouvelle Aquitaine, La Rochelle, France, Sept/2021, E. Thinon

Pole 3 – Biophysics

Mass Spectrometryof Nucleic Acids & Supramolecular Complexes

- Journées Françaises de Spectrométrie de Masse, online, 06/2021, S. Benabou
- Kyoto-Bordeaux symposium, online, 02/2021, V. Gabelica
- Bordeaux symposium on foldamers, Bordeaux, France, 09/2021, V. Gabelica
- 2nd Scientific Meeting of the GDR RNA, Online, 10/2021, S. Benabou

Solid-state NMR of Molecular Assemblies

- Journée Maladies du Bois de Vigne, Reims, November, A. Loquet
- ACS Spring, Virtual, April, A. Loquet

Conference Organisation

Pole 4 – Molecular & cellular biology

Control & dynamics of cell division

- GSO, Carcassonne, October 2021, A. Royou

Novel mediators in lung oncogenesis

- 17th GSO Canceropole 2021, Carcassonne, France, November 2021, D. Santamaría
- SifrARN postponed to 2022, Bordeaux/France, October 2022, C. Di Primo
- Joachim Frank Honorary Symposium, Columbia Unversity, NYC, NYC, USA, September, 2022, Y. Hashem
- The Ribosome Conference, Bordeaux, France, 2022, Jully 10– 14, 2022, Y. Hashem
- EMBO YIN Microbiology Sectoral Meeting, Bordeaux, France, December 2021, A. Innis
- Biologie Structurale Intégrative (BSI), scientific committee member, Paris-Saclay, France, November 2021, V. Gabelica
- Foldamer 2021, Bordeaux, France, September 2021, G. Guichard
- Transatlantic Quebec/Nouvelle Aquitaine Network in Functional Materials: Focus on Energy and Health applications – 48th IUPAC World Chemistry Congress, Montreal, Canada (virtual), August 2021, G. Guichard

Access to the platform:

The platform is accessible to researchers from the public and from the private sector. All information on available equipment and process to request services or contact experts can be found on the BPCS web page:
http://www.iecb.u-bordeaux.fr/index.php/en/structural-biophysico-chemistry

Three types of services are offered:

(1) Instrument access time: duly trained users can request machine time, perform the experiments, and interpret the data. Office space is available to accommodate external users.

(2) Routine services: samples are submitted, the platform personnel performs the assays and sends the analysis report to the user. Experiments for which the data interpretation is routine fall into this category.

(3) Collaborative projects: all requests that require the platform personnel's scientific expertise and/or methodological developments in instrumentation, experiment design, or data interpretation, fall into this category (Bordeaux Recherche Oncologie).

Technology Platforms

Dr. Brice Kauffmann
Head of IECB's Biophysical and Structural Chemistry platform, IR, CNRS

Head of IECB's Biophysical and Structural Chemistry platform, IR, CNRS After a PhD in protein crystallography (2003, University of Nancy I), Brice Kauffmann spent three years at the European Molecular Biology Laboratory (EMBL) in Hamburg (Germany) working on the development of a new macromolecular crystallography beamline (X12, DESY). He joined the European Institute of Chemistry and Biology in January 2006 as a staff Scientist.

Selected publications

1. Winnerdy FR, Bakalar B, Das P, Heddi B, Marchand A, Rosu F, Gabelica V, Phan AT. Unprecedented hour-long residence time of a cation in a left-handed G-quadruplex. Chem Sci. 2021 Apr 26;12(20):7151-7157.
2. Atcher J, Mateus P, Kauffmann B, Rosu F, Maurizot V, Huc I. Large-Amplitude Conformational Changes in Self-Assembled Multi-Stranded Aromatic Sheets. Angew Chem Int Ed Engl. 2021 Feb 1;60(5):2574-2577.
3. Latxague L, Benizri S, Gaubert A, Tolchard J, Martinez D, Morvan E, Grélard A, Saad A, Habenstein B, Loquet A, Barthélémy P. Bolaamphiphile-based supramolecular gels with drugs eliciting membrane effects. J Colloid Interface Sci. 2021 Jul 15;594:857-863.
4. Daskalov A, Martinez D, Coustou V, El Mammeri N, Berbon M, Andreas LB, Bardiaux B, Stanek J, Noubhani A, Kauffmann B, Wall JS, Pintacuda G, Saupe SJ, Habenstein B, Loquet A. Structural and molecular basis of cross-seeding barriers in amyloids. Proc Natl Acad Sci U S A. 2021 Jan 5;118(1).
5. Delannoy López DM, Tran DT, Viault G, Dairi S, Peixoto PA, Capello Y, Minder L, Pouységu L, Génot E, Di Primo C, Deffieux D, Quideau S. Real-Time Analysis of Polyphenol-Protein Interactions by Surface Plasmon Resonance Using Surface-Bound Polyphenols. Chemistry. 2021 Mar 22;27(17):5498-5508.
6. Liu P, Battie Y, Decossas M, Tan S, Pouget E, Okazaki Y, Sagawa T, Oda R. Chirality Induction to CdSe Nanocrystals Self-Organized on Silica Nanohelices: Tuning Chiroptical Properties. ACS Nano. 2021 Oct 26;15(10):16411-16421.

Biophysical & Structural Chemistry platform (BPCS)

IBiSA-labelled since 2011, IECB core facility provides privileged access to state-of-the-art instruments and dedicated scientific expertise from scientists leading research programs either at IECB or in partner labs on the Bordeaux campus. The BPCS serves to nucleate the development of a supportive local community with expertise in structural biology, structural chemistry and biophysics to increase the attractiveness of the University of Bordeaux for talented scientist from all over the world.

In 2019, the IECB core facility has joined the new "Core Facilities" department at Bordeaux University. At the forefront of methodological developments in Structural (Bio) Chemistry and Biophysics, the facility is gathering on the same site a coherent set of techniques and expertise to investigate molecular recognition processes and structure of supramolecular assemblies from a structural and biophysical perspective.
Importantly, the facility stands at the frontiers between chemistry and biology, by focusing both on biological molecules and on synthetic molecules conceived to fold and self-assemble like biological molecules and/or interact with biological systems. It is indeed not sufficient to determine simply the structure and biochemical properties of macromolecules in vitro. In line with the trend towards systems biology and integrated structural biology initiatives in Europe (Instruct), a major challenge now is to understand how macromolecules functions dynamically within a larger macromolecular assembly or in a cellular pathway or even at the organism level. Understanding dynamical processes is not possible using a single technology, but becomes potentially accessible through the integration of a number of approaches, spanning different resolution scales. The IECB facility follows that development strategy by regrouping expertise and state-of-the art instruments in Biochemistry (production and purification of recombinant proteins, peptide synthesis…), NMR spectroscopy (liquid and solid state with 8 spectrometers from 100 MHz to 800 MHz), X-ray crystallography (from crystallization to atomic resolution structure on single crystals or powder samples with a high flux X-ray source and Hybrid direct detector), Cryo-EM (with a 200kV FEI Talos Arctica microscope equipped with a GATAN K2 summit camera), mass spectrometry (the facility has a strong specificity in studying non-covalent complexes by ion mobility mass spectrometry with an Agilent 6560 ESI-IMS-Q-TOF), surface plasmon resonance and spectroscopy (absorption and circular dichroism spectroscopy, SPR exploiting a T200 instrument from Biacore).

Access to the platform:
The platform is accessible to researchers from the public and from the private sector. All information on available equipment and process to request services or contact experts can be found on the BPCS web page:
http://www.iecb.u-bordeaux.fr/index.php/en/structural-biophysico-chemistry

Three types of services are offered:
1. Instrument access time: duly trained users can request machine time, perform the experiments, and interpret the data. Office space is available to accommodate external users.
2. Routine services: samples are submitted, the platform personnel performs the assays and sends the analysis report to the user. Experiments for which the data interpretation is routine fall into this category.
3. Collaborative projects: all requests that require the platform personnel's scientific expertise and/or methodological developments in instrumentation, experiment design, or data interpretation, fall into this category.

Organization

Biophysical and Structural Chemistry Platform (BPCS)
Scientific direction : Valérie Gabelica – Antoine Loquet
Technical coordination : Brice Kauffmann

Certification ISO9001 - NFX50-900
Loïc Klinger (AI) **RMQ**

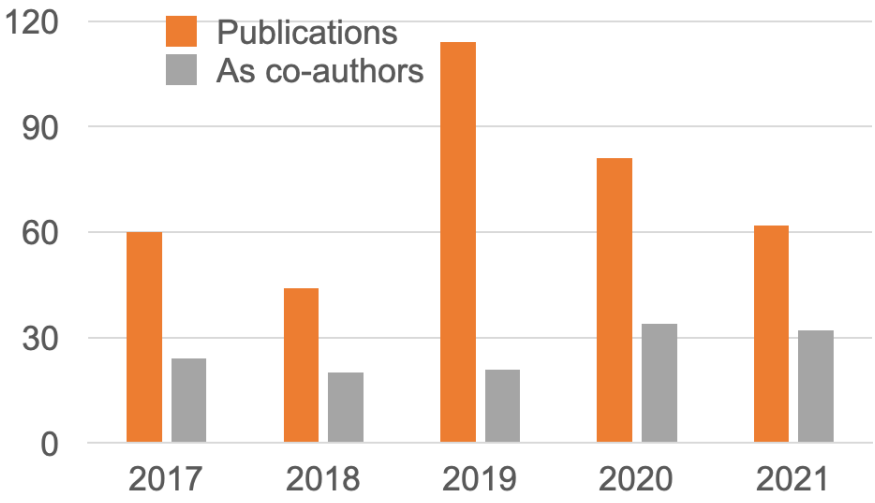
NMR	Cryo-EM	X-ray	Mass Spec	Protein prod	SPR-CD	Pept. synth.
Staff E. Morvan (IE) A. Grelard* (IR) **Expert** A. Loquet	**Staff** Site B14 M. Decossas* (IR) S. Tan* (AI) Site B13 N… (IR demandé) **Experts** Y. Hashem R. Fronzes	**Staff** B. Kauffmann (IR) S. Massip (IE) **Expert** G. Guichard	**Staff** F. Rosu (IR) C. Buré (IR, àpd 06/2022) **Expert** V. Gabelica	**Staff** L. Bataille (IR) JM. Blanc (IE) T. Dakhli (Tech) M. Mederic (Tech) **Expert** A. Loquet	**Staff** L. Minder (AI) **Expert** C. Di Primo	**Staff** L. Klinger (AI) **Expert** G. Guichard

* Personnels CBMN – UMR5248

2020 Highlights:

Recruitment of a staff scientist, expert in protein expression and purification
In late 2021, thanks to the University of Bordeaux, Laure Bataille was recruited as IR2 at the UAR3033. At the BPCS Laure will bring almost twenty years of experience in academia and private companies on protein production and purification.

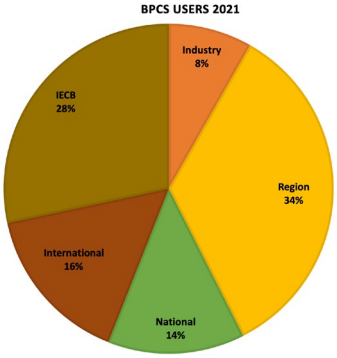
A new Hybrid pixel detector and robot for high throughput on the crystallography facility
With a consolidated budget of 150 k€ assembled in 2021 (thanks to IBiSA, CNRS INC, University of Bordeaux (FED), INSERM and partner lab CBMN) a new pixel Hybrid detector and a crystallization robot for high throughput screening will be installed early 2022.



Figures for 2021

Users of the platform: In 2021, the platform contributed to **134** projects for more than **60** different public or private laboratories or companies.

Key figures:
- **More than 100** people **trained** per year (students, technicians, researchers)
- **62** publications with staff members as co-author or with acknowledgments for the BPCS.



Technology Transfer & Start-ups

The scientific breakthroughs achieved at IECB are meant to nurture technological innovation. The skills, knowledge and technologies developed at the institute are transfered to economic players via different routes:

Collaborative research

Servier, UreKa, DART Neurosciences... Several key industry players work with IECB teams.

Contract services and consulting

The IECB brings together a wide range of scientific equipments and expertise in chemistry and biology. Such resources are made available to public and private research centers through IECB's Biophysical and Structural Chemistry platform.

Technology transfer

IECB researchers are strongly encouraged to patent their discoveries.

The technology transfer unit Novaptech that was hosted at IECB in 2008-2013 is now a promising biotech company headquartered in Bordeaux.

Incubating start-ups

IECB has 300 m2 work space dedicated to start-ups. Ureka created in 2010 is located at the institute since 2014. Until 2018, a part of this area was also occupied by Fluofarma, created in 2003 by two team leaders from IECB.

Dr. Sébastien Goudreau
Ureka Research Director

Year of creation 2010

Staff 5

Website www.urekapharma.com

Contact
sebastien.goudreau@immupharma.com

Established in the region of Bordeaux since March 2014, UREkA, a subdivision of ImmuPharma, propose to revolutionize the way we make peptide-based drugs.

Coming from the vision of Robert Zimmer, director of ImmuPharma and Gilles Guichard, professor at the IECB, UREkA is the result of many years of research of foldamer chemistry in the laboratory of Gilles Guichard. UREkA is now performing research programs to apply its UrelixTM technology for the discovery of innovative therapeutics in close collaboration with IECB group leader Gilles Guichard.

Medicinal chemistry – diseases of interest

- Diabetes
- Hypoglycemia
- Obesity
- Non-alcoholic steatohepatitis (NASH)
- Cancer

Collaborative research projects

- Implementation of Urelix™ technologies in partners projects.
- Design and synthesis of bioactive foldamers.
- Hit to lead
- SAR
- Development

Scientific Events

Workshops & symposia held at IECB

Scientific seminar of the Bettencourt Schueller Foundation laureates in Bordeaux

October 26

Symposium Ki-NOA 2021

November 29

Invited Speakers:
Thomas Barois
Thierry Buffeteau
Marie-Hélène Delville
Lucie Fisher
Valérie Gabelica
Claude Geffroy
Eric Grelet
Alexander Kuhn
Yann Mairesse
Sébastien Papot
Emilie Pouget
Guillaume Raffy
Vincent Rodriguez
Baptiste Vignolle

Symposium on Foldamers

September 13-14-15

Invited Speakers:
Lukasz Berlicki
Peter Crowley
Felix Freire
Valérie Gabelica
Tom Grossmann
Nathalie Katsonis
Tamas Martinek
Siibren Otto
Anja Palmans
Frank Würthner

Inauguration of Axel Innis' laboratory, equipped thanks to the 2017 "Bettencourt Coup d'élan pour la recherche française » prize

October 25

Seminars

1. Dr. Hervé Vezin (CNRS – Laboratoire Avancé de Spectroscopie pour les Interactions la Réactivité et l'Environnement (LASIRE), Université de Lille).
   Title: Advanced EPR spectroscopy in material chemistry for batteries.

2. Dr. Hagen Hofmann (Department of Structural Biology, Weizmann Institute of Science).
   Title: Allostery through DNA drives phenotype switching.

3. Prof. Camilo Perez (Biozentrum, University of Basel).
   Title: Structure and mechanism of a proton dependent lipid transporter involved in lipoteichoic-acids biosynthesis.

4. Dr. Michael Eck (Dana-Farber Cancer Institute and Harvard Medical School).
   Title: Insights into regulation of the Ras/Raf/MAPk pathway from Cryo-EM Structures of BRAF-MEK-14-3-3 Complexes.

5. Dr. Stephan Rauschenbach (University of Oxford).
   Title: Electrospray ion beam deposition for single molecule imaging.

6. Prof. Bernard Rentier (Recteur Honoraire, Université de Liège).
   Title: Open Science: Excellence revisited.

7. Dr. Nora Vazquez-Laslop (University of Illinois at Chicago).
   Title: Macrolide antibiotics as modulators of translation.

8. Dr. Abhishek Chatterjee (Department of Chemistry, Boston College).
   Title: Genetically encoded chemistries to read and write biology.

9. Dr. Julien Gronnier (Center for Plant Molecular Biology, University of Tübingen).
   Title: Nanoscale regulation of cell-surface receptor signaling.

10. Dr. Jonathan Visentin (CHU de Bordeaux, Université de Bordeaux, Immuno ConcEpT, UMR CNRS 5164).
    Title: Surface plasmon resonance to study anti-HLA antibodies: transfer of a basic science method to the bedside of organ transplant recipients and beyond.

11. Prof. Pierre Sonveaux & Prof. Raphaël Frédérick (Université catholique de Louvain).
    Title: Discovery of an oxidative pathway of lactate in cancer and its druggability by inhibitors of lactate dehydrogenase 1 (LDH1) oligomerization.

12. Dr. Alexander Harms (Biozentrum, University of Basel).
    Title: Drop out or go viral: A story of planned and unplanned expeditions into the phage world.

13. Dr. Eric Cornes (Institute Pasteur).
    Title: Non-coding small RNAs as versatile regulators of germline gene expression programs.

14. Dr. Jacob Bobonis (EMBL Heidelberg).
    Title: Bacterial retrons encode phage-sensing toxin/antitoxin systems.

15. Dr. Benoit Malleret (National University of Singapore).
    Title: Molecular mechanisms of Plasmodium vivax invasion and cell tropism of zoonotic malaria species.

16. Prof. Valérie de Crécy-Lagard (University of Florida).
    Title: Linking gene and function by comparative genomics: examples from deazapurine metabolism reveal cross-talks between RNA and DNA modifications.

17. Dr. Vishukumar Aimanianda (Institut Pasteur).
    Title: Fungal cell-wall polysaccharides, exploiting their translational potential.

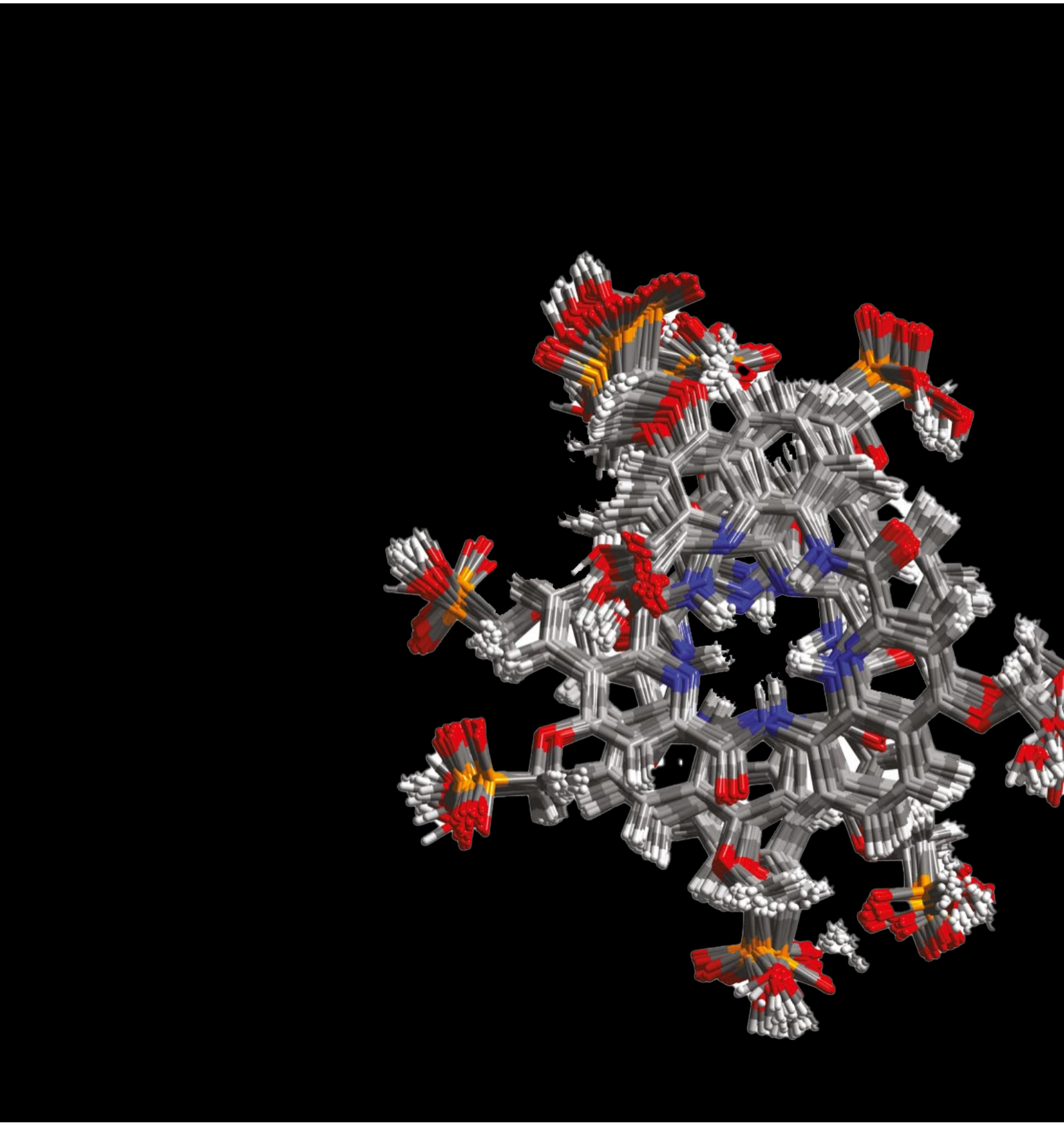
18. Dr. Niels Fischer (Max Planck Institute for Biophysical Chemistry, Germany).
    Title: Single particle cryo-EM – Towards atomic-resolution of molecular machines in motion.

19. Dr. Megan Wright (University of Leeds, UK).
    Title: Chemical proteomic tools to study host-microbe interactions.

Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

I E C B



Institut Européen de Chimie et Biologie
2, rue Robert Escarpit
33607 Pessac FRANCE

Tél. : +33(0)5 40 00 30 38
Fax. : +33(0)5 40 00 30 68
www.iecb.u-bordeaux.fr